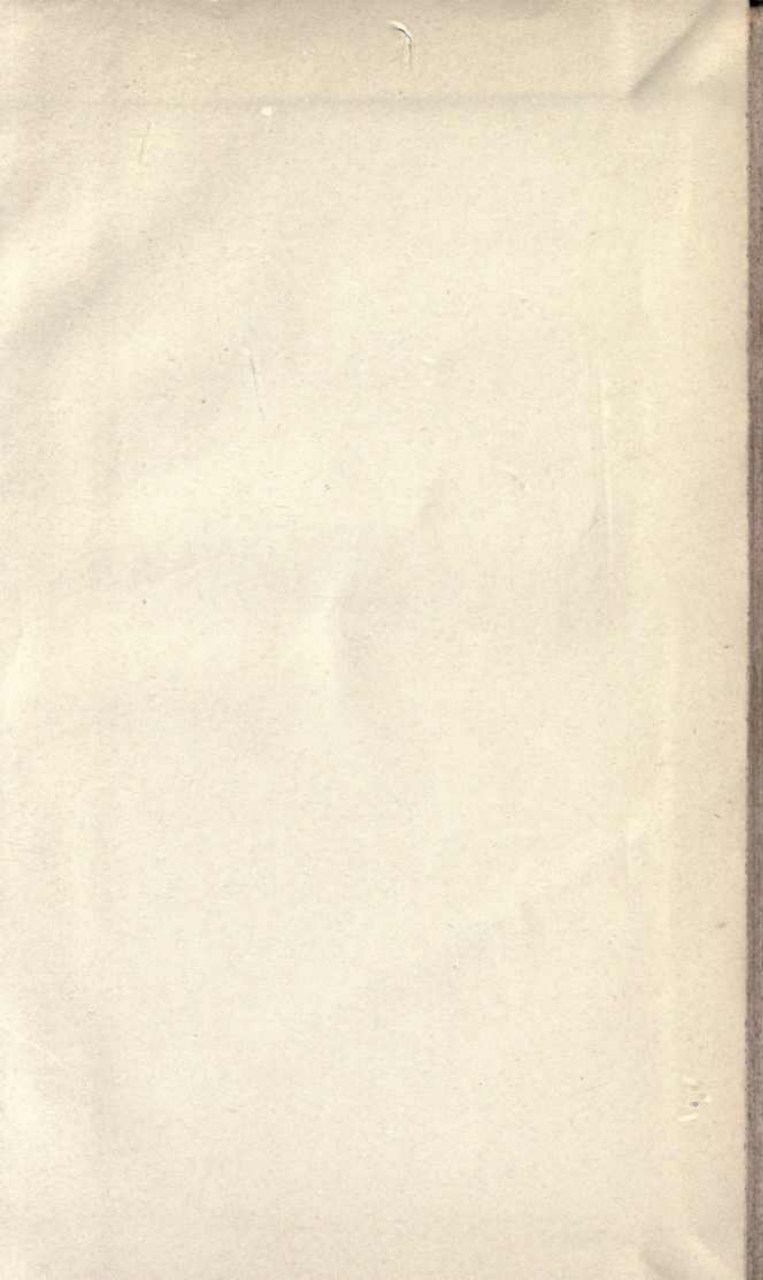
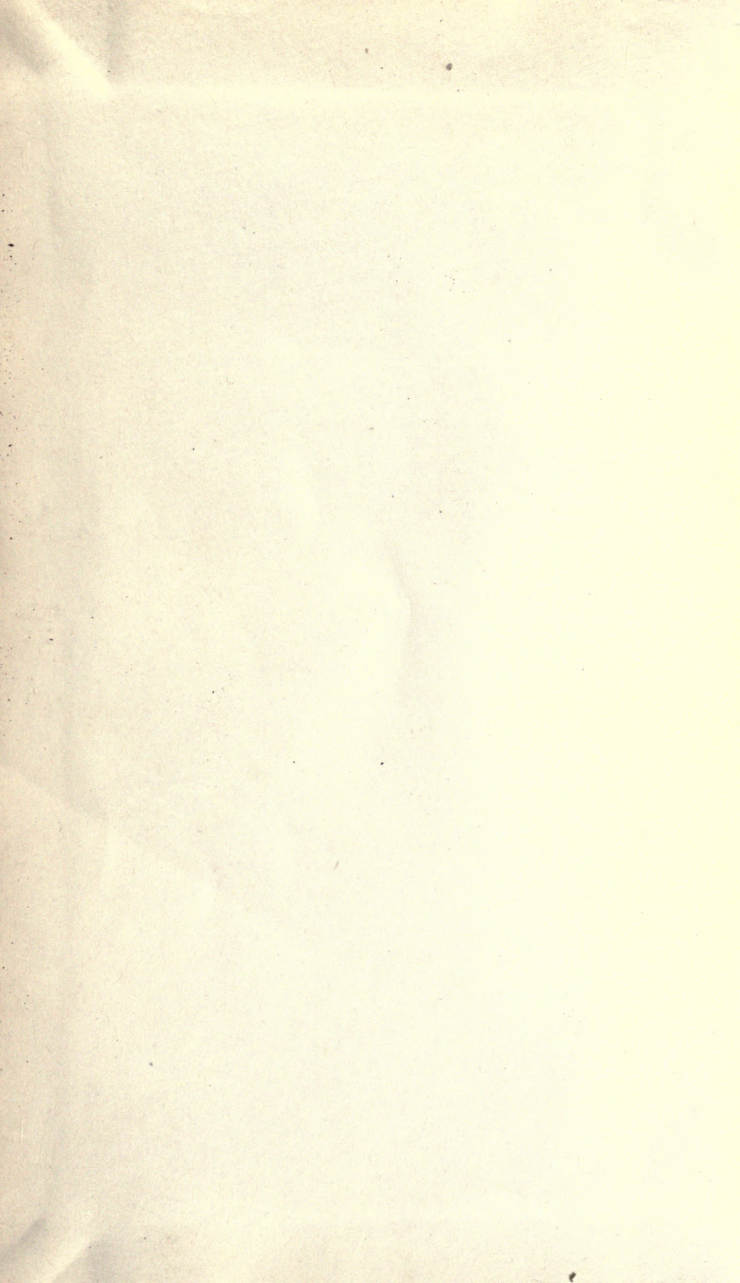


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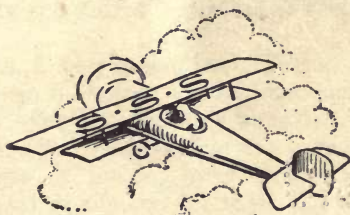
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PREFACE

THIS book is an attempt to describe as briefly as possible how the body works. It is definitely addressed to those who are already acquainted with the elements of the subject, and is intended to supplement the larger text-books. In writing it I have therefore omitted to describe the physical and chemical processes upon which physiology is so largely based, and I have assumed that the reader is familiar with the experiments commonly performed in the elementary class. For the same reason I have treated histology only incidentally, and have not described systematically the general structure of the central nervous system.

I admit to a plagiarism from Foster in the opening words. I know no better way of introducing the subject.

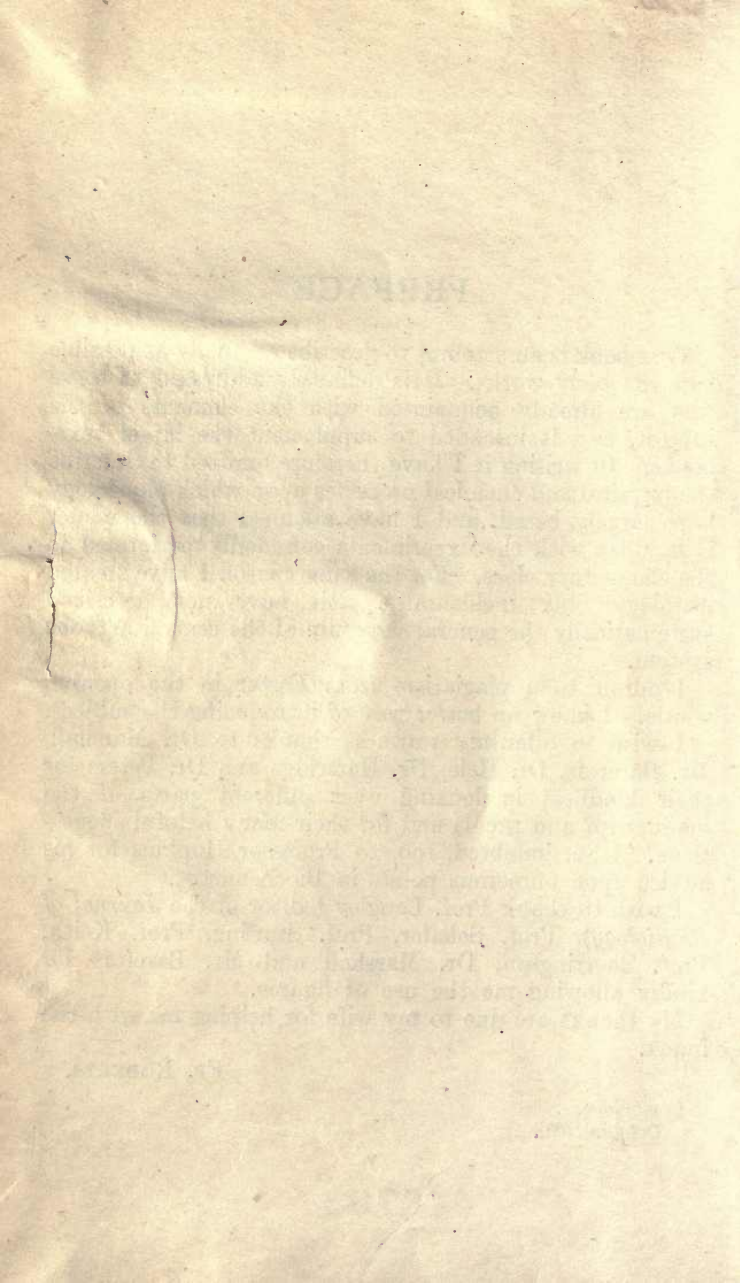
I wish to offer my warmest thanks to Dr. Marshall, Mr. Barcroft, Dr. Hele, Dr. Hartridge and Dr. Peters for their kindness in looking over different parts of the manuscript and proofs and for their many helpful suggestions. I am indebted, too, to Professor Hopkins for his advice upon numerous points in Biochemistry.

I wish to thank Prof. Langley (editor of the *Journal of Physiology*), Prof. Schafer, Prof. Starling, Prof. Keith, Prof. Sherrington, Dr. Marshall and Mr. Barcroft for kindly allowing me the use of figures.

My thanks are due to my wife for helping me with the index.

FF. ROBERTS.

Cambridge,
October 1920.



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SYNOPSIS OF PHYSIOLOGY

CHAPTER I

INTRODUCTION

WHEN a single-celled organism such as *Amœba* is studied it is found to possess certain features which distinguish it from non-living things. (1) It is able to change its shape, to envelop particles of food-material and to move from place to place. These functions it performs by virtue of the **contractility** of the protoplasm of which it is composed. (2) It responds in an **active** manner to certain stimuli. It has therefore the property of **irritability**. (3) It has the power of ingesting or dissolving particles of certain organic substances and of incorporating them into its own architecture. This is the process of **assimilation** or **anabolism**. (4) It is also able to oxidise the complex substances formed in anabolism. This process is known as **catabolism**, the combined processes of anabolism and catabolism being termed **metabolism**. (5) It is able to expel from its body certain substances. These are of two kinds—particles which it has enveloped but cannot digest, and end-products of the catabolic changes. This function is known as **excretion**. (6) Lastly, it has the capacity for **reproducing itself**.

These fundamental properties are found also in multicellular animals, but with this difference, that in the latter the different cells of which the individual is composed

have become specially endowed with one or other of these properties. In other words, there is a **division of labour**, all the cells contributing their share for the good of the whole, the cells which possess the same property being grouped together into units known as tissues. The muscular tissues are cells specialised in contractility; the nervous tissues in irritability; the digestive tissues in assimilation. Special tissues exist also for excretion and reproduction.

Yet, though the one property has been exalted at the expense of the others, these have not entirely disappeared. All cells are assimilative; muscle, though primarily contractile, is irritable. Those properties other than the one which is characteristic of the tissue have sunk to a secondary position—they may be latent, but they are not necessarily completely abolished.

From the grouping together of a number of cells certain consequences follow. The first is the *need for binding the cells together*. A number of structures are developed to play this passive rôle. Such are the connective-tissues—bones, ligaments, and fibrous tissue. The second consequence is that as the individual increases in size the number of cells which are in direct contact with the surrounding medium becomes smaller. In *Amœba*, the cell being completely surrounded with water, there is ample opportunity for interchange of food and excretions. In multi-cellular organisms, on the other hand, only the few cells on the surface can be nourished and drained in this way. As a means of overcoming this difficulty there is developed a **transport system—the blood**. Each cell in our bodies is bathed in a salt solution just as freely as though it floated independently, and this salt solution brings it the nourishment which it needs and removes the waste products which it excretes.

In the animal economy a factor of supreme importance is the *rapidity of the circulation*. This is what we are most apt to forget—possibly because we are unconscious

of the movement of our own blood. Yet over four litres are leaving each ventricle per minute and passing through the aorta with a velocity of about eighteen centimetres per second.

The rapidity with which the blood flows and its indiscriminate distribution among the tissues have certain important results. Any abnormality in the metabolism of one tissue immediately affects, through the blood, the whole body. While the circulation is free there can be no localisation of a substance soluble in the blood. This freedom of the circulation is made use of for the purpose of co-ordinating the activities of the different organs. In the first place, the accumulation of *normal* products of metabolism leads to a series of changes in other organs. In the second place, certain organs have become specialised solely to produce substances which quicken or retard some general bodily function. These substances are known as *internal secretions* or *hormones*.

This chemical method of co-ordination has at once an advantage and a disadvantage. The advantage lies in the nicety of adjustment which is possible, due partly to the potency of the chemical substance formed, partly to the sensitiveness of the organ upon which it acts. The respiratory centre, for instance, is a far more delicate indicator of the reaction of the blood than any known chemical reagent. Again, adrenalin exerts its effects in the strength of one part in a million. The disadvantage of the chemical method is the time which it takes to work its effects. Rapid as the circulation is, it is not sufficiently rapid for the proper co-ordinated response where time is an important factor.

For rapid co-ordination Nature makes use of the irritability of protoplasm. The nerve cells, some of them cells of great length, are specially adapted to conduct disturbances arising in one part to different parts of the body. The grouping of nerve cells to form the central nervous system is for the purpose of effecting rapidly, in response

to a change in the environment, an appropriate physiological reaction.

One difference, then, between the chemical and the nervous co-ordination is a difference of speed. Another difference lies in the greater variety of response which the intricate nature of the nervous system makes possible.

It is sometimes stated that life is simpler in a single-celled than in a multi-cellular animal. It may be questioned which is the more complex, an organism in which different functions are pigeon-holed in different tissues, admirably co-ordinated though these be, or an organism in which all the animal functions are performed in an orderly manner in one cell. Specialisation of function does not necessarily mean greater complexity of the biological process. In what sense, then, is a multi-cellular animal such as a mammal "higher" than a unicellular organism such as *Amœba*? Simply in this, that with division of labour goes an increase of stability in face of changes in the environment, an increase in the power of response to external disturbing factors, an indifference to adverse circumstances. The *Amœba* is completely at the mercy of the slightest changes in the physical and chemical condition of the water in which it lives. Its hold upon life is of the slenderest. Contrast with this the comparative security of life possessed by the mammal. In the following pages we shall have reason to see the extraordinary stability possessed by different bodily systems. The reaction of the blood, the volume of the blood, the arterial blood-pressure are, within wide limits, maintained constant in spite of external forces tending to disturb them. Another example is seen in the regulation of body temperature.

But the most potent factor in the stabilising of the body is the evolution of the central nervous system—the development of instincts, memory, association of ideas, and other intellectual processes. It is to the greater security of life

which these bring that man owes his pre-eminent position among all living beings. The problem before us is to show the bodily mechanisms by which man triumphs over his environment.

The study of function in the higher animals will therefore have to be considered from three aspects:—

1. The mechanism possessed inherently by each organ, *e.g.* the mechanism of the heart-beat.
2. The co-ordination of different mechanisms into bodily functions, *e.g.* the co-ordination of heart, lungs and brain in the supply of oxygen to the tissues during exercise.
3. The protective reactions of the body to changes in its environment.

In the following pages we shall try to develop the study of function from this threefold point of view.

CHAPTER II

ENZYMES

A LARGE number of the chemical changes which occur in living tissues can be imitated in the laboratory only by means of high temperatures or violent reagents. Without these the changes occur at so slow a rate that they can be practically regarded as not occurring at all. Such reactions can, however, be brought about with great rapidity in the presence of certain substances which can be prepared from the living cells. These substances, which in the living body are responsible for facilitating otherwise difficult reactions, are called enzymes or ferments. Enzymes may act either within or without the cell in which they are produced—a distinction of no biological significance.

Enzymes do not influence the energy changes which are inherent to the reactions which they bring about. Although it is possible that they act by forming compounds with the substrate (as the substance upon which they act is called), such compounds have but a momentary existence, the enzymes appearing at the end of the reaction unaltered, unless they happen to be destroyed by a secondary reaction. *Enzymes merely change the rate of a reaction.*

It is clear from the above description that the part played by enzymes corresponds to that played by catalytic agents in inorganic reactions. Enzymes may indeed be defined as *catalysts produced by living tissues*.

As to the chemical constitution of enzymes, little is known. They are definitely not protein. They contain nitrogen and probably a carbohydrate group.

Physically, enzymes belong to the emulsoid class of

colloids. When in "solution" in water they exist as particles containing a small amount of water suspended in water. Some of their properties are, as we shall see, referable to their colloidal nature. There is considerable evidence to show that they act by providing a large surface upon which the molecules of the substrate are adsorbed. The concentration of the substrate thus brought about leads, by the law of mass action, to the acceleration of a reaction which otherwise would take place only at an infinitely slow rate. In favour of the existence of adsorption compounds as an intermediate stage, is the fact that sometimes an enzyme is more resistant to heat when in presence of its substrate. Again, the fact that certain enzymes may function even in a medium in which they are insoluble, is best explained on the assumption that adsorption compounds are formed.

In their surface effects enzymes strongly resemble the metals in a finely divided state. Colloidal platinum effects a rapid combination of hydrogen and oxygen; colloidal iron greatly accelerates the oxidising action of hydrogen peroxide.

We now have to consider the factors which influence enzyme action, showing how they lend support to the idea that enzymes are colloidal in structure and catalytic in function.

1. *The effect of temperature.*—At $0^{\circ}\text{C}.$, enzymes are reduced to inactivity, but are not destroyed. As the temperature rises they become more active. This, however, is only one particular instance of the general rule that molecular activity increases with rise of temperature. At a temperature equal to or slightly above body-temperature, enzymes display their maximum activity. This is the so-called *optimum temperature*. Beyond this point their activity wanes, owing to their gradual destruction.

Destruction by heat does not constitute any distinction between enzymes and inorganic catalysts. It is a property of the enzyme, which is shared by some inorganic catalysts of colloidal nature—for instance, colloidal platinum.

2. *The action of electrolytes.*—All enzymes are very sensitive to the reaction of the medium in which they work. There is for every enzyme a certain H-ion concentration in which it displays a maximum activity. This is readily understood when we consider the effect of electrolytes upon the colloid particles. Agglomeration of particles must lead to diminution of surface upon which adsorption can take place.

3. *Specificity.*—This is a characteristic feature of enzymes. Each enzyme brings about only one kind of reaction, and acts either upon only one particular substance or only one class of substances. Enzymes are indeed commonly named after the bodies upon which they act. There are the proteolytic enzymes, which hydrolyse proteins; lactase, which acts upon lactose; arginase, which hydrolyses arginine. In this respect enzymes differ from inorganic catalysts only in degree. The specificity of enzymes is not absolute, as was once supposed. Further, specificity is found among inorganic catalysts, although to a far less extent.

The high specificity of enzymes is believed by some to depend upon a close structural resemblance between enzyme and substrate, these fitting like lock and key. The view is also held that an enzyme consists of two parts—an active principle related structurally to the substrate, and a non-specific colloid which merely serves to provide a surface upon which the active principle can come into contact with the substrate.

4. *Reversibility of Action.*—When a reaction is reversible, an inorganic catalyst which quickens it in one direction quickens it in the other to the same extent. The catalyst, therefore, does not influence the equilibrium point. For instance, in the reaction—

Ethyl acetate + water \rightleftharpoons ethyl alcohol + acetic acid,

the equilibrium-point is the same whatever the amount of the catalyst HCl present. It depends only upon the relative velocity of the two reactions, that is to say, upon

the active mass of the components of the system. If water is present in abundance, the equilibrium-point will be almost at complete hydrolysis. But if ethyl acetate be removed from the system as soon as it is formed, complete synthesis will take place.

The question now arises whether enzymes behave like inorganic catalysts in this respect. Many reactions occur reversibly in the body: the saponification and synthesis of fats; the interconversion of glycogen and glucose. Reversibility of action has been proved for certain enzymes, particularly for maltase and lipase. It is therefore probable that in the body an enzyme accelerates a reversible reaction in both directions, but that the actual change which takes place depends upon the removal of certain products from the sphere of action as soon as they are formed. When fat is saponified in the intestine by the action of lipase the process is complete, because the products of saponification are rapidly absorbed. Within the intestinal epithelium these accumulated products are resynthesised, probably by the lipase which formed them.

5. *Velocity of Reaction*.—When the amount of enzyme is small compared with the amount of substrate, the rate of reaction is, in the initial stages, directly proportional to the amount of enzyme, and independent of the amount of substrate. The enzyme, in other words, can only deal with a certain amount of substrate at a time. But the final result, given sufficient time, is the same whatever the amount of enzyme; that is to say, there is no quantitative relation between the amount of enzyme and the amount of substrate. This constitutes a useful criterion in deciding whether a substance is a ferment or not.

When the amount of enzyme is relatively large, the velocity of the reaction undergoes a progressive diminution. This is to be expected from the law of mass action, since the concentration of the substrate is undergoing a constant diminution. The falling off, however, is usually more rapid than would be expected from theoretical considera-

tions. Several factors contribute to this. There is the gradual development of the reverse reaction. The enzyme may be killed by the products of its own action. Again, the products may cause a change in the reaction of the medium which itself inhibits the action of the enzyme. In the tryptic digestion of proteins, for instance, the amino-acids formed, being many of them distinctly acidic, increase the H-ion concentration, and thus tend to retard the action of the enzyme.

Is all metabolic activity due to the action of enzymes? At present this question cannot be answered decisively. There are certain reactions which can be brought about by living cells, but not by enzymes. No enzymes, for instance, have been discovered in the mammary gland capable of forming the organic constituents of milk. Again, antiseptics of a certain concentration are lethal to protoplasm but not to enzymes. It is possible that all stages exist between simple enzyme action and protoplasmic activity.

CHAPTER III

BLOOD

WHEN blood is centrifugalised, means having been taken to prevent it clotting, it separates into three layers: the lowest layer composed of the red corpuscles in an almost solid mass; above this a thin layer consisting of the leucocytes; above this, again, a clear fluid, the blood-plasma.

THE PLASMA

Blood-plasma has a specific gravity of 1.06.

Its saline constituents amount to 0.85 per cent. Of these, the most abundant is sodium chloride; potassium, calcium, magnesium, phosphates, carbonates and sulphates also occur.

Plasma contains the following proteins—

1. Fibrinogen, belonging to the class of globulins.
2. Serum-albumin.
3. Serum-globulins $\left\{ \begin{array}{l} \text{euglobulin.} \\ \text{pseudoglobulin.} \end{array} \right.$
4. (?) Thrombogen.

Besides the above substances, plasma contains dextrose fats, cholesterin, lecithin, urea and other nitrogenous substances, amino acids and innumerable substances of unknown composition such as antitoxins.

THE RED BLOOD CORPUSCLES

Structure and Composition

The *Red Blood Corpuscles*, of which there are about 5,000,000 to every c.mm. in men and rather less in women,

are circular, biconcave, non-nucleated discs of a yellowish colour. They consist of a stroma containing hæmoglobin. This is probably surrounded by an envelope of lecithin and cholesterin. The corpuscles are flexible, and by altering their shape can squeeze through apertures smaller than themselves. They are pervious only to substances

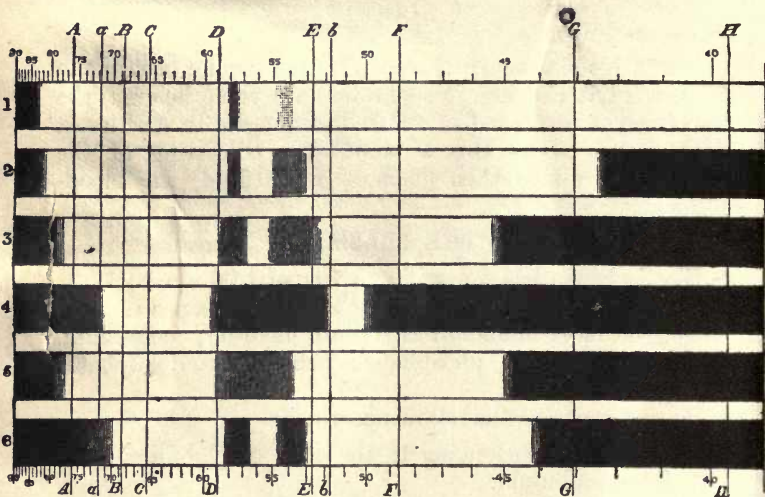


FIG. 1.—The spectra of hæmoglobin and its derivatives. 1–4, Oxy-hæmoglobin in increasing concentration; 5, reduced hæmoglobin; 6, carboxyhæmoglobin. (After Preyer and Gamgee, from Starling's *Principles of Physiology*.)

such as alcohol, chloroform, urea, which are soluble in lecithin and cholesterin. They are impervious to inorganic salts. In standing blood the corpuscles tend to clump together into *roulettes*. Concentration of the saline constituents of the plasma causes a shrinking of the corpuscle, while dilation causes the reverse, viz. swelling up and bursting with liberation of the hæmoglobin. The latter process, known as “hæmolysis,” can also be brought about by treat-

ment with ether, bile salts and the serum of an animal of a different species.

The *stroma* consists of nucleoprotein, lecithin and cholesterol. *Oxyhæmoglobin*, the loose combination of hæmoglobin and oxygen, can be obtained in crystalline form. It has a molecular weight of about 16,600 and contains .3 per cent. of iron. It is easily dissociated into hæmoglobin and oxygen. The oxygen can be replaced by carbon monoxide, which forms a far more stable compound. The absorption bands of hæmoglobin and its derivatives are seen in Fig. 1. *Oxyhæmoglobin* gives a narrow band at λ 579, and a broader band at λ 544. Reduced hæmoglobin gives a broad band at λ 555. *Carboxyhæmoglobin*, which is brighter in colour than *oxyhæmoglobin*, resembles spectroscopically *oxyhæmoglobin*, but both bands are slightly nearer the red end, and the second band is better defined.

Methæmoglobin, isomeric with *oxyhæmoglobin*, is, however, a more stable compound. It occurs pathologically wherever there is excessive breakdown of red blood corpuscles. Its importance lies in the fact that it can be formed by treating hæmoglobin with potassium ferricyanide. Although the resulting product contains the same amount of oxygen as *oxyhæmoglobin*, the original oxygen of the *oxyhæmoglobin* is quantitatively liberated. This is, therefore, a method for *determining the amount of oxygen in blood*.

It has been suggested that *oxyhæmoglobin* has the formula—



while *methæmoglobin* has the formula—



Hæmoglobin is composed of hæmatin ($\text{C}_{34}\text{H}_{34}\text{N}_4\text{O}_5\text{Fe}$),

and a protein, known as globin. While the composition of hæmatin is constant, the globin varies in different animals.

Life-history

Nucleated red corpuscles circulate in the human embryo as early as the third week. From the eighth week, non-nucleated cells begin to take their place. By the time of birth, nucleated forms have disappeared.

The corpuscles first appear in the yolk sac, and soon after in the chorion and wherever blood-vessels are being formed. Their development is indeed contemporaneous with that of the blood-vessels, both being derived from the same syncytial masses of mesoderm. From the tenth day, the liver is for some time the seat of formation, while after the sixth week, the same function is performed by the spleen. By birth the seat of formation is transferred to the red bone-marrow, where it remains throughout life. Here all stages of formation can be seen in the cells between the blood sinuses. The activity of the marrow is increased by hæmorrhage, diminished by impoverisation of the diet. When the formation of corpuscles is rapid, nucleated forms (erythroblasts) appear in the blood.

After circulating in the blood for an unknown period, the corpuscles are destroyed by phagocytes, chiefly in the spleen and hæmolymph glands. The liberated hæmoglobin is transferred to the liver, where it is decomposed and the hæmatin formed converted into the bile-pigments, *bilirubin* and *biliverdin*. These are excreted in the bile into the duodenum. They are partly converted into *stercobilin*, the colouring matter of the fæces, partly reabsorbed and excreted in the urine as *urobilin*.

THE LEUCOCYTES

The leucocytes normally number from 6000–8000 per c.mm. of blood. The number is increased during digestion and in nearly all inflammatory conditions.

Classification

The following different kinds of leucocytes are described.

1. *Polymorphonuclear Cells*.—In size $10-12\mu$. The nucleus varies considerably in shape, being usually either three-lobed or horse-shoe. The cell-body contains fine granules, which stain, some with acid, others with basic dyes, the result on double staining giving a purple effect. Hence the name neutrophile sometimes given to them. These cells are actively amœboid. They constitute 60-70 per cent. of the total leucocytes.

2. *Coarsely-granular or Eosinophile Cells*.—In size and in the shape of the nucleus, these resemble the polymorphonuclear cells. They differ from them in containing coarse granules, which stain deeply with eosin. They are only found to the extent of 1 per cent.

3. *Lymphocytes*.—These are smaller than the above varieties, having a diameter of 7.5 . The cell is spherical and is almost filled with the nucleus, which is often kidney-shaped. The cytoplasm stains a pale blue, and is free from granules. Occasionally large forms are seen. These cells are not amœboid. About 25 per cent. of the leucocytes are of this class.

4. *Mononuclear or Hyaline Cells*.—These are large—up to 25μ , and round or ovoid in shape. The nucleus is ill-defined and feebly staining. The cell-body is slightly basophile and non-granular. The cells are slightly amœboid. These form about 2 per cent. of the leucocytes.

5. *Basophile or "Mast" Cells*.—In size they are about 10μ . The nucleus is tri-lobed, and the cell-body contains basophile granules. They are difficult to find, forming less than 1 per cent.

Origin of the Leucocytes

The polymorphonuclear cells and probably the eosinophiles are formed in the bone-marrow from large cells known as myelocytes. The lymphocytes are formed in

“lymphoid” tissue, which is widely distributed throughout the body—particularly in relation to the alimentary canal—the tonsils, adenoids, and Peyer’s patches. The thymus, the Malpighian corpuscles of the spleen, and the lymphatic glands are tissues of the same nature. In all these organs lymphocyte-formation by mitosis can be seen.

Functions of the Leucocytes

Besides circulating in the blood, leucocytes wander through the intercellular spaces of the tissues. Their function is the destruction and digestion of foreign bodies, such as bacteria, and the absorption of tissues which are undergoing degeneration. This process is known as *phagocytosis*. In acute inflammatory conditions, there is a mobilisation of leucocytes, particularly of the polymorphonuclear variety, at the site of infection, and an increase in the number circulating in the blood.

The ingestion of foreign bodies is carried out by the polymorphonuclear and mononuclear cells. The part played by the lymphocytes is unknown. They increase in number in chronic affections such as tuberculosis. It is believed that from the granules of the coarsely granular cells, both oxyphile and basophile, are excreted substances which are toxic to bacteria.

BLOOD-PLATELETS

These are small bodies 1–5 μ in diameter. In form, size and number they vary according to the way in which the blood has been collected. They are usually circular discs, containing fine granules. They number from 100,000–500,000 per c.mm. In the circulating blood they are only seen when the vessel-wall is injured. When blood is carefully collected, and kept at body temperature, no platelets can be found. It is therefore believed that they are not present in normal circulating blood. How they are produced is uncertain, some observers believing that they arise from the disintegration of red-cells and leucocytes.

Whatever their origin may be, they seem to play, as we shall see, an important part in the process of coagulation. They seem to be absent from avian and probably from amphibian blood.

The *specific gravity of blood*, measured by taking the specific gravity of a mixture of chloroform and benzene, in which blood neither rises nor sinks, varies in man between 1057 and 1066—slightly less in women.

The *viscosity*, measured by its rate of flow through a capillary tube, is five times that of water. It varies with the number of red corpuscles.

The *amount of hæmoglobin* is best measured by the Haldane-Gowers Hæmoglobinometer. Blood diluted 200 times is saturated with CO and the colour tested against a sample made up from a mixture of blood (similarly treated) from a number of healthy individuals.

Proportion of Corpuscles to Plasma.—The proportion of corpuscles to the total volume of blood is measured by the *hæmatocrit*. This is a graduated tube, in which blood can be centrifugalised. The corpuscles which settle at the bottom form normally about 37 per cent. of the volume of the blood.

Number of Corpuscles.—This is estimated by means of the Thoma-Zeiss hæmatocytometer.

REACTION OF THE BLOOD

The reaction of the blood is most conveniently expressed in terms of the concentration of hydrogen ions. Pure water is very slightly ionised into hydrions and hydroxyl-ions—



at 21° C. the concentration of H and OH being *each* 10^{-7} gramme-ions per litre. If an acid such as HCl be added, this is to a large extent dissociated into H- and Cl-ions. The H-ions in the system are therefore increased, let us say, to 10^{-5} , the OH-ions being decreased, to a corresponding extent, to 10^{-9} . When an alkali is added the reverse takes place. An acid is therefore a solution which has at 21° C. a H-ion concentration greater than 10^{-7} , and an alkali is one which has a H-ion concentration less than 10^{-7} . The differ-

ence between a strong and a weak acid is due to the greater degree of ionisation of the former.

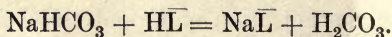
It is usual to express the hydrogen ion concentration as the logarithm to base 10 of the hydrogen ion concentration, according to **Sørensen's** method, the negative sign being omitted for simplification. This figure is known as the " P_H ."

When the H-ion concentration is 1×10^{-7} normal, $P_H = 7.0$. When it is 0.2×10^{-7} normal, $P_H = 7.7$.

$$\begin{aligned} & \text{(Since } \log 10^{-2} = 0.30 \\ \therefore 0.2 \times 10^{-7} &= 10^{30-70} = -7.7). \end{aligned}$$

In the case of blood, $P_H \cdot 7.0$ and $P_H \cdot 7.7$ are the limits compatible with health. The figure for P_H *decreases* as the H-ion concentration (and therefore the acidity) *increases*.

When an acid is added to the blood the H-ion concentration is not raised to anything like the same amount as occurs when the acid is added to water. The stability of the blood in this respect is called **buffer action**. Buffer action may therefore be defined as the capacity to take up acid without acquiring a corresponding acidity. The substances responsible for buffer action, themselves known as buffers, are chiefly inorganic salts, and to a less extent proteins. Of the salts the most important is NaHCO_3 , which for practical purposes may be considered to be the only "buffer" normally called into play. When an acid such as lactic is added to blood the following reaction occurs—



Since carbonic acid is hardly ionised at all, there is practically no change in P_H .

A solution of NaHCO_3 always contains a certain amount of CO_2 dissolved in it, and the P_H of such a solution is determined by the ratio $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$. When, therefore, lactic acid is added to *circulating* blood, the diminution in the

NaHCO_3 which we have seen take place would lead to a decrease in P_H were it not for the fact that the body possesses three methods for restoring the ratio $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$, and so keeping the P_H constant.

1. The *respiratory centre* is extremely sensitive to the H-ion concentration of the blood supplying it, responding to the slightest increase by increasing the pulmonary ventilation. This reduces the CO_2 in the alveolar air and therefore the CO_2 of the blood.

2. The *kidney* responds to increased H-ion concentration

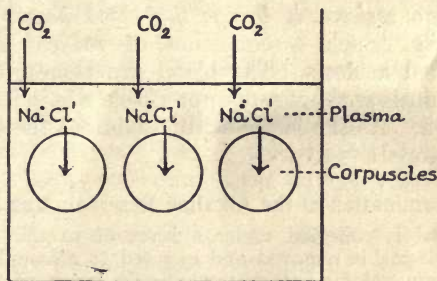


FIG. 2.—Migration of chlorine ions.

by excreting acid sodium phosphate until the normal reaction is restored.

3. The *blood itself* responds by an interaction of ions between plasma and corpuscles. When CO_2 is added to the blood, chlorine ions migrate from the plasma to the corpuscles, thus, as it were, releasing sodium to combine with CO_2 . This transference of chlorine ions is connected with the fact that reduced hæmoglobin (reduced in this case in consequence of the addition of CO_2) is less acid than oxyhæmoglobin. The migration of chlorine ions from plasma to corpuscles has the effect of increasing the NaHCO_3 of the plasma by an amount corresponding to the increase in CO_2 .

It will therefore be seen that the blood has the power of carrying a varying amount of acid with practically no change in the H-ion concentration, and that this power depends almost entirely upon the *buffer action* of NaHCO_3 . We see further that the blood possesses a store of NaHCO_3 , a store fluctuating in amount. Sodium bicarbonate is therefore termed the **alkaline reserve**. It serves the purpose of *stabilising* the H-ion concentration. When a more stable acid such as lactic appears in the blood, it combines with sodium and therefore reduces the amount of NaHCO_3 . In small amounts this causes only a very slight change in the H-ion concentration, but by reducing the alkaline reserve *it brings the blood nearer the margin of stability*. Such a condition of *reduced alkaline reserve* is called **acidosis**. The blood can therefore be in a state of acidosis without any appreciable rise in its H-ion concentration. As the lactic acid is oxidised the alkaline reserve is restored.

Determination of the Alkaline Reserve : Van Slyke's Method

Blood is collected under a layer of paraffin and centrifuged. The plasma is removed and exposed to a sample of alveolar air. A known volume is then treated with excess of 5 per cent. H_2SO_4 , frothing being prevented by addition of a drop of caprylic alcohol. It is then put under reduced pressure and the CO_2 driven off is measured. Since this is the CO_2 combined chemically in the plasma, the amount of NaHCO_3 can be calculated.

Determination of H-ion Concentration

Electrical Method.

Sørensen's Method.—The plasma is treated with an indicator, *e. g.* neutral red, and the colour matched with a series of phosphate solution.

Barcroft's Method.—This depends upon the fact that H-ion concentration determines the form of the dissociation curve of oxyhæmoglobin (p. 101).

THE TOTAL AMOUNT OF BLOOD IN THE BODY

This is estimated by two methods.

1. Haldane's Carbon-monoxide Method

This method depends upon the fact that carbon monoxide combines with hæmoglobin to form a compound more permanent and of a brighter tint than oxyhæmoglobin. The following are the steps in the process—

1. The oxygen capacity of the subject's blood is first determined—that is to say, the amount of oxygen with which 100 c.c. of blood can combine. This is estimated most accurately by an indirect method. The oxygen capacity of ox blood is determined directly by the ferri-cyanide method. By means of the hæmoglobinometer, the hæmoglobin content of the ox blood and of the subject's blood are compared. From this is calculated the oxygen capacity of the subject's blood. Suppose 1 c.c. of blood combines with a c.c. of oxygen.

2. The subject breathes a known volume (V) of carbon monoxide. This turns out some of the oxygen from combination with hæmoglobin.

3. The percentage saturation of the blood with CO is determined in the following way. A sample of blood taken before CO inhalation, (A), and a sample taken after, (B), are diluted to the same amount. The latter will be slightly redder than the former. Another sample (C), similarly diluted, is saturated with CO by bubbling coal-gas through it. This, of course, will be redder still. Carmine is now added to A from a burette until the colour is the same as B. Let the amount of carmine used be x . Addition of carmine is then continued until the colour equals that of C. Let the total amount of carmine added be y .

The amount of CO required to saturate the blood completely would therefore be $\frac{y}{x} \times V$. Now a given weight of hæmoglobin combines with the same volume of oxygen as it does with carbon monoxide. The amount of oxygen required to saturate the whole of the hæmoglobin is there-

fore $\frac{y}{x} \times V$ c.c. But we already know that 1 c.c. of blood combines with a c.c. of oxygen.

The volume of blood is therefore $\frac{\frac{x}{y} \times V}{a}$.

2. Vital-red Method

Vital-red is a non-toxic dye, which on injection colours the plasma, but does not to any extent affect the corpuscles.

A known volume of dye, say 15 c.c., is injected into a vein, a sample of blood being drawn before and after the injection. Both samples are centrifugalised, and the plasma separated from the corpuscles. Two solutions are now made up as follows—

Standard. $\left\{ \begin{array}{l} 1 \text{ part plasma before injection of dye.} \\ 1 \text{ part dye solution diluted 200 times with} \\ \quad \text{isotonic NaCl.} \\ 2 \text{ parts isotonic NaCl.} \end{array} \right.$

Test. $\left\{ \begin{array}{l} 1 \text{ part plasma after injection of dye.} \\ 3 \text{ parts isotonic NaCl.} \end{array} \right.$

The intensity of the coloration of the two solutions is then compared, that of the test being expressed as a percentage of that of the standard.

It is clear that if the two colours are of equal strength, the total volume of plasma must be 15×200 c.c. = 3 litres.

If R is the percentage reading of the test solution, the volume of plasma = $\frac{100}{R} \times \text{No. of c.c. of dye injected} \times 200$.

From the volume of plasma, the volume of the blood is obtained by means of the hæmatocrit.

Prior to the discovery of these methods, the only estimations of the amount of human blood were derived from

experiments upon executed criminals. From these, the weight of the blood had been found to be one-thirteenth of the body weight. Haldane, however, puts the figure at one-twentyfifth.

When the volume of the blood is disturbed, the body reacts so as to restore it to its normal value. When fluid enters the body from the intestine, it does not materially increase the blood-volume, for the excess is immediately excreted by the kidney. When blood is lost by hæmorrhage, the volume is recovered by the passage of fluid from the lymph spaces into the circulation, the normal number of red corpuscles being restored later by increased activity of the bone-marrow.

At high altitudes the volume of the blood is diminished, with the result that there is a relative concentration of red blood corpuscles. This effect comes on within twenty-four hours. After a few weeks the number of red corpuscles is increased absolutely by heightened activity of the bone-marrow.

THE COAGULATION OF BLOOD

The clotting of blood consists in the deposition in it of a meshwork, consisting of a protein known as fibrin. In this meshwork the corpuscles are entangled and from it exudes a fluid—the serum. Clotting is essentially the formation of fibrin.

The conditions which determine the occurrence or non-occurrence of fibrin-formation are very diverse.

The process is hastened in drawn blood—

1. By mechanical disturbance;
2. By keeping it at body temperature;
3. By addition of serum or clot;
4. By addition of extracts of nuclear tissue;

and *in vivo*—

5. By injury to the endothelial lining of the blood-vessel.

The process is retarded or prevented—

1. By addition of sodium oxalate, fluoride or citrate ;
2. By cooling ;
3. By receiving it direct from the interior of a blood-vessel into a vessel lined with paraffin ;
4. By addition of leech extract.

If freshly drawn blood is treated with sodium oxalate, fluoride or citrate, it fails to clot. Clotting can be induced by addition of calcium in excess. Calcium, therefore, is necessary for the formation of fibrin, the preventive action of the oxalate and fluoride being due to the metal being precipitated, that of the citrate being due to the metal being converted into a non-ionised form.

From the oxalated plasma there can be precipitated, by half-saturation with sodium chloride, a protein—*fibrinogen*. This, on being separated and redissolved, forms fibrin as soon as calcium is added to it. Fibrinogen, then, is or contains the precursor of fibrin.

If fibrinogen be purified by repeated precipitation, it no longer clots on addition of calcium. *Crude* fibrinogen, therefore, contains another substance essential to clotting.

Purified fibrinogen, on addition of serum or clot in the absence of calcium, readily clots.

Purified fibrinogen, on the addition of fresh oxalated plasma, does not clot.

From the above facts, these inferences can be drawn.

1. There is present in clot and serum, but not in fresh blood, a substance which directly causes clotting, even in the absence of calcium.

This substance is called *thrombin*.

2. Thrombin is evidently the substance removed from crude fibrinogen in the process of purification.

3. Calcium is necessary, not for the conversion of fibrinogen into fibrin, but for a process anterior to this, the formation of thrombin, from a parent-substance (*thrombogen* or *prothrombin*).

Thrombin was at one time universally believed to be a ferment. There is evidence, however, that thrombin unites quantitatively with fibrinogen. It is probably a protein.

We have already seen that when blood is drawn direct from the blood-vessel into a vessel lined with paraffin—that is to say, without touching any tissue—clotting is retarded. In the bird, under the same circumstances, it is prevented altogether. In blood drawn in this way, clotting can be readily induced by addition of almost any tissue-extract, or of blood-clot. But if tissue-extract is added to pure fibrinogen, clotting does not occur. The substance present in tissue-extract is therefore not thrombin, though its presence is necessary for the formation of thrombin. In the formation of thrombin, therefore, two factors are necessary, calcium and the substance present in tissue-extract. The latter is a ferment called *thrombokinase*. Thrombokinase, in addition to being present in tissues, occurs also in the blood platelets, or rather, it would be more accurate to say, is produced in the formation of the platelets. The absence of platelet-formation in the bird is the reason why uncontaminated blood does not clot in these animals.

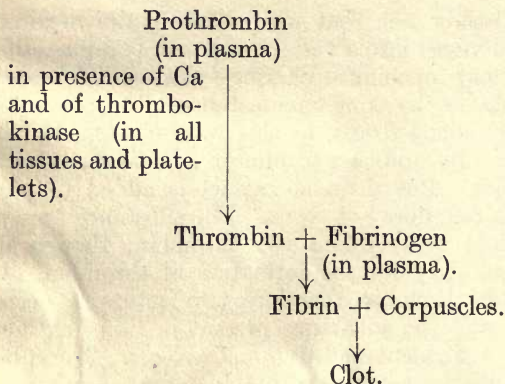
The argument may be summarised thus: clotting takes place in two stages: (1) the formation of thrombin from thrombogen (present in plasma), by the action of the ferment thrombokinase (present in tissues and blood-platelets), in the presence of calcium. (2) The interaction of thrombin and fibrinogen to form fibrin.

The view has been expressed that thrombokinase is not a specific substance, the formation of thrombin being attributed to the effect of the calcium ions upon the colloidal thrombogen in the presence of any fine particles, such as dust.

To explain why clotting does not occur in the intact circulation, we must assume either that the endothelial lining of the vessels is devoid of thrombokinase, or that an antithrombin is present. A similar hypothetical anti-

thrombin must be credited to the salivary glands of the leech.

The process of coagulation may be tabulated thus—



THE LYMPHATIC SYSTEM

In all parts of the body, with the exception of the spleen-pulp, the tissue-cells are bathed in a fluid—the lymph (Fig. 3). This is contained in irregular spaces separating the cells from one another, and from the walls of the blood-capillaries. Through the lymph nutritive substances pass from the blood to the cells, and waste-products pass from the cells to the blood.

Lymph originates in the blood-plasma. It is continually passing in and out through the capillary walls. A certain amount, however, regains the blood indirectly by a system of vessels—the lymphatics—comparable in structure to the veins. Lymph-capillaries originate in the intercellular spaces and join together to form larger vessels which again unite to form on each side a duct which drains into the blood at the junction of the subclavian and jugular veins. The two ducts are very unequal in size and in the territory from which they gain tributaries. That on the left is much

the larger, and is known as the *thoracic duct*. It drains the left side of the head and neck and thorax, the left upper and both lower limbs, and the whole of the abdomen with the exception of the upper surface of the liver. The remainder of the body is drained by the *right lymphatic duct*.

The lymphatics originate not only in the interstitial spaces of the tissues, but also in the serous membranes such as the pleura, pericardium and peritoneum, and from the joints.

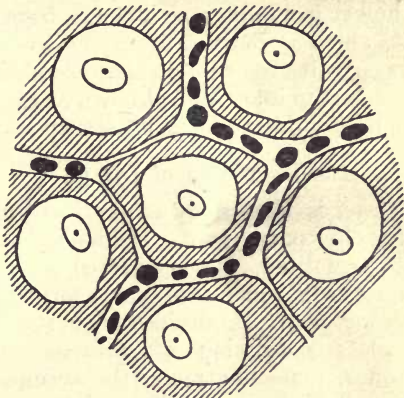


FIG. 3.—Showing diagrammatically the relation between cells, capillaries and lymph. The lymph is shaded. The capillaries are shown, some contracted, some distended.

In the villi of the small intestine they arise as the *central lacteals*. In this region the lymphatics have the special function of transporting fat from the intestinal epithelium.

In some part of their course the larger lymphatic vessels are interrupted by the *lymphatic glands*. These consist of masses of lymphocytes enclosed in a fibrous capsule. The lymphocytes are here being formed; they pass into the circulation by the efferent lymphatics.

The flow of lymph along the lymphatics is very slow. Even the thoracic duct only pours out about 1 c.c. per

minute. The rate of flow from any tissue varies with physiological activity. When the body is at rest there is practically no flow from the limbs, all the lymph being derived from the viscera, particularly the liver.

Properties of Lymph

Lymph is usually a clear, alkaline fluid which clots slowly on standing. It contains the same saline constituents as blood plasma. Its protein content varies with its origin, being much higher in lymph which comes from the viscera than in that which is derived from the limbs. Normal lymph always contains less protein than blood. The lymph which comes from the intestine is known as *chyle*. During digestion it is milky, due to fat held in suspension.

The Formation of Lymph

Whether lymph is formed by a physical process or by secretion is an old controversy. Heidenhain argued that it was due to secretion. He discovered that there were certain substances which increased lymph formation. These he called *lymphagogues*. He divided them into two classes—the first class consisting of protein substances—such as peptones, mussel-extract; the second class consisting of crystalloid bodies such as dextrose and urea. Both these classes owed their effect, Heidenhain believed, to a stimulating action upon the secretory process.

Foremost amongst the opponents of this view is Starling. According to Starling, the action of the first class of lymphagogues can be discounted because these substances are toxic. The action of the second class is due to a disturbance of osmotic relations. When these substances are injected they raise the osmotic pressure of the blood and thus cause withdrawal of water from the lymph-spaces into the blood. As they themselves, being slightly diffusible, pass into the lymph-spaces they cause a flow by osmosis in the opposite direction—in this way causing an increased flow of lymph.

Under normal conditions, according to Starling, lymph formation is influenced by two factors—the state of the blood and the state of the tissue. As to the blood, the lymph is exuded from it owing to the capillary pressure. When this increases, other things being equal, the amount of lymph formed increases also. In confirmation of this, Starling found that the rate of lymph flow from the liver was increased when the venous outflow was obstructed, and diminished when the arterial supply was lowered. It can, however, be argued that this effect is produced indirectly by the altered metabolism due to the stagnation of the blood. It is known that deficient oxygenation causes an excessive flow of fluid into the tissue spaces (**Œdema**).

But the effect of blood pressure is partly counterbalanced by the osmotic pressure of the plasma colloids, which pass but slowly through the capillary walls. The importance of the osmotic pressure of the plasma proteins as a factor in restraining the passage of fluid from the blood is shown by the therapeutic effect of infusions for severe hæmorrhage. It is now agreed that isotonic saline is of little use for this purpose, since, owing to the dilution of the plasma proteins, capillary pressure exceeds osmotic pressure, so that all the fluid injected passes into the tissues. To be retained, the injecting fluid must have an osmotic pressure equal to that of plasma. To this end a 6 per cent. solution of gum arabic is used. *The effective force driving the lymph out of the capillaries is therefore the capillary pressure minus the difference between the osmotic pressure of the plasma proteins and the osmotic pressure of the lymph proteins.*

But while this force drives the lymph *a tergo*, another draws it *a fronte*. This is the activity of the tissue-cells. In every tissue lymph-formation increases with activity. In the limbs lymph only flows when the muscles are working. Starling explains the coincidence of lymph-flow with activity in this way. When the cells become active, large molecules are broken down into smaller ones. The osmotic pressure within the cells and tissue-spaces is thus raised.

This attracts fluid from the blood and causes an increase of lymph. The difference in the amount and character of lymph from the abdominal viscera and from the limbs is explained by assuming that the capillaries of the former are the more permeable.

In the central nervous system the place of the lymph is taken by the **cerebrospinal fluid**. It contains a small amount of sugar but is almost free from proteins. Secreted by the choroid plexus into the third ventricle, it passes by the foramen of Majendie in the roof of the fourth ventricle into the subarachnoid space. It passes into the cerebral veins by the Pacchionian bodies.

THE SPLEEN

In the splenic pulp the blood-vessels take the form of sinuses, the walls of which are incomplete. The blood, therefore, passes out and mixes with the splenic cells. This is the only situation in the body where the blood comes into direct contact with tissue-cells without the intervention of lymph.

In the adult spleen, two processes can be seen to take place—destruction of red blood corpuscles and formation of lymphocytes. The first is carried out by large phagocytic cells, which engulf and digest the red cells. The hæmoglobin is not destroyed in the spleen, since destruction of injected hæmoglobin is unaffected by removal of the organ. It is carried by the splenic vein to the liver, where it is converted into bile-pigment.

The formation of lymphocytes takes place in the *Malpighian corpuscles*, which are masses of lymphoid cells situated around the small arteries and undergoing proliferation. Blood in the splenic vein is said to contain more leucocytes than blood in the splenic artery.

In foetal life the spleen is said to be one of the seats of formation of red cells. Whether this function is continued after birth is a matter of dispute. Normally, no histological

evidence of it can be made out, but it is said that after severe loss of blood, red cells are to be seen in process of formation. When the spleen is removed, there occurs a diminution in the red cells of the circulating blood—a fact which indicates either that the spleen does normally form these cells, or that it provides a hormone which stimulates this function elsewhere.

The high content of purine bases which occurs in the spleen is incidental to the metabolism of leucocytes. There is no evidence that, apart from this, the spleen has a special function of purine formation.

The slow rhythmic contractions which the spleen undergoes by virtue of its unstriated muscle-fibres, are evidently for the purpose of propelling the blood through the organ. The spleen cannot form a reservoir for excess of blood.

From the fact that life can be continued normally after removal of the spleen, it is clear that whatever function it performs can be transferred to other organs. Of these the most important are probably the *hæmolymp h glands*, which, scattered throughout the abdomen, are intermediate in form between the spleen and the lymphatic glands.

CHAPTER IV

CONTRACTILITY

Introduction

CONTRACTILITY is one of the fundamental attributes of protoplasm. It is the means whereby the organism changes its size and shape, and in the animal world its position in space. It is seen in its simplest form in the *Amoeba*, where by retraction here and protrusion there of the undifferentiated protoplasm surrounding the nucleus the animal is enabled to ingest foreign particles and move from one place to the other. This simple mode of locomotion is known as amoeboid movement. Even in the highest organism this method is retained. It is found for instance in the leucocytes of the blood and in the pigment layers of the retina.

Ascending in the animal scale we find certain cells specialised to effect, through changes in their shape, movements of certain organs or of the whole organism, such movements showing the widest variation in their strength and rate. This capacity for change in shape is associated with the presence of fibrils which are laid down in the cell substance. The fibrils are known as *sarcostyles*, and the protoplasm in which they lie, *sarcoplasm*. The cells in which the power of contraction is most strongly developed are characterised by a great complexity of the *sarcostyles*.

Broadly speaking, two types of muscle cell are found, the unstriated and the striated, these terms being referable to the absence or presence of transverse-striation in the

fibres. These two classes show certain differences in form, mode of contraction and function. The structural differences will be dealt with more fully in a subsequent paragraph. It is only necessary to point out here that in unstriated muscles the fibres are believed to be connected to one another by fine bridges of contractile tissue, the consequence being that a state of contraction is propagated from fibre to fibre throughout the whole muscle. In striated muscle, on the other hand, each fibre receives a nerve filament and is independent of its neighbours. On account of this difference between the two types, an unstriated muscle always contracts as a whole, whereas in striated muscle the contraction can be graded by varying the number of fibres brought into play.

As to the form of contraction, striated muscle differs from unstriated in its greater rapidity and force of contraction. The other difference between striated and unstriated muscle lies in their relation to the central nervous system. The striated are usually, but not always, under the control of the will. The unstriated are not directly under voluntary control; they usually subserve visceral functions. The striated, highly specialised though they are in contractile power, are incapable of any form of contraction except in obedience to impulses arriving from the nervous centres, and, owing to a constant flow of impulses, they are normally in a condition of partial contraction or **tonus**. Cut off from these impulses, they become flabby or toneless. Unstriated muscles on the other hand have in large measure retained a power of contraction independent of outside influences. Like the striated, they are normally in a state of tonus, but the tonus *is an inherent property of the muscles themselves*, being independent of impulses arriving from the nervous centres. Besides tonus, they often possess a power of rhythmic contraction, an example of which is seen in the muscle of the intestinal wall. But though capable of contraction independently of the nervous system, their tonus and rhythm are still

subject to control by impulses arriving from the nervous centres, these impulses serving either to increase or to decrease the degree of tonus and the rate and force of the rhythmic contractions.

Commonly, unstriated muscles are supplied by two different nerves, one augmenting, the other suppressing a pre-existing state of activity. Herein lies another distinction between the two classes, for variations in the contraction of striated muscles are brought about, so far as is known, only by variation in one direction or the other of a constant flow of impulses *along one and the same nerve*.

Heart muscle occupies an intermediate position between the two classes. Structurally it exhibits a faint cross-striation and continuity from cell to cell. It resembles unstriated muscle in its rhythmic power, in its independence of the central nervous system, and in its double nerve-supply. It resembles striated muscle in the strength of its contraction.

Composition of Muscle

If muscle-tissue be minced at 0° C., extracted with NaCl solution and the mixture filtered, a filtrate is obtained which consists of an opalescent fluid—*muscle plasma*. This consists of two proteins, an albumin and a globulin, which have been called *myosinogen* and *paramyosinogen* respectively. On slightly raising the temperature this fluid, like blood-plasma, undergoes coagulation, the two proteins being converted into an insoluble form—*fibrin*. From being neutral or slightly alkaline, the reaction becomes acid—a change attributable to the development of *sarcolactic acid*. The residue which is left behind on the filter-paper consists principally of what may be called the incidental constituents of muscle—fibrous and nuclear material and sarcolemma.

The serum which can be squeezed out of the muscle clot consists of a pigment, *myohæmatin* (related to hæmo-

globin), extractives, creatine, hypoxanthine and xanthine, fats, glycogen, inosite (the so-called muscle-sugar, but in reality a benzene derivative), and lactic acid.

When muscle loses its blood-supply it soon undergoes a profound physical change. From being translucent and elastic it becomes opaque and stiff. This alteration, like the clotting of muscle plasma, is accompanied by a development of sarcolactic acid. The condition which the muscle assumes is termed **rigor mortis**. A similar change may be brought about if the muscle is slowly warmed above the coagulation temperature of its proteins. Since the most striking chemical change is the development of lactic acid, the question arises whether the presence of this acid is the cause or the result of the physical alteration in the muscle. Lactic acid increases in muscle as the result of activity, and the rate of onset of rigor is dependent upon the degree of accumulation of the acid. Further, rigor can be prevented even in a dead muscle if the accumulation of acid is prevented by perfusion. The formation of lactic acid, then, would seem to be the forerunner and the cause of rigor.

Structure of Muscle

Unstriated muscle is composed of fusiform cells of variable length. There is an oval nucleus. The sarco-plasm is occupied with fibrils disposed longitudinally.

Striated muscle consists of fibres of 0.05 mm. diameter and of varying length up to 3 cm. Each fibre is enveloped in an elastic sheath, the sarcolemma. It is composed of discs or sarcomeres of dark and light material alternately—an arrangement which gives to this type of muscle its name. In the middle of each light band is a row of granules constituting the so-called *Krause's membrane*. The complete disc therefore consists of a dark middle portion and a light portion at each end, Krause's membrane being the surface of union of adjacent discs. Each of these discs is broken up longitudinally into a number of longitudinal fibrillæ,

the sarcostyles, which are separated from one another by a granular substance—sarcoplasm.

The relative amount of sarcostyle and sarcoplasm in a fibre is variable, and confers upon the fibre its form of contraction. Where the sarcoplasm is scanty (*white fibre*), the contraction is in the form of a rapid twitch; where abundant (*red fibre*), the contraction is slow and sustained. While in some animals individual muscles are composed exclusively of either red or white fibres, in man both types of fibre are often found in the same muscle. There is some evidence to show that both sarcostyle and sarcoplasm are endowed with contractility, the movement being rapid in the case of the former, slow in the case of the latter.

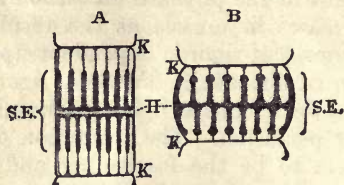


FIG. 4.—Sarcomere (diagrammatic). A, relaxed; B, contracted. K, membrane of Krause; H, line of Henle; S.E., sarcostyle (Schafer)

When a muscle-fibre is observed under the microscope the act of contraction is seen to consist of a broadening of the fibre and a thinning of the individual discs. At the same time the dark band becomes lighter and the light band darker, until a complete reversal is obtained. When, however, the fibre is observed through polarised light the dark bands are anisotropic, or doubly refracting, appearing light; while the light bands are isotropic, or singly refracting, and appear dark. In contraction there is no reversal of this effect, but an increase of the anisotropic at the expense of the isotropic substance.

In the following pages we shall deal primarily with striated muscle, indicating how cardiac and unstriated muscle resemble or differ from it.

The Irritability of Muscle

Striated muscle retains, to a considerable degree, the primitive characteristic of protoplasm in general—irritability—though this is normally masked by the superior irritability of nerve. The inherent irritability of muscle is shown by the occurrence of contraction in strips of muscle demonstrably free from nervous element. It is shown most perfectly by Claude Bernard's classical experiment. In a frog both sciatics were exposed and a ligature tied round the right thigh so as to include all tissues except the nerve. Curare was then injected into the lymph sacs. In a few minutes stimulation of the left sciatic nerve was without effect upon the gastrocnemius, while on the right side a normal contraction was evoked. On both sides the muscles continued to respond to direct stimulation. The drug had therefore paralysed neither the muscles nor the nerve-trunk, since the muscles had been exposed to its action on the left side and the nerve-trunk on both sides. It had acted upon the nerve-endings in the muscles. These having been put out of action, direct stimulation affected the muscle itself.

CHANGES ACCOMPANYING CONTRACTION

The changes which a muscle undergoes when it passes from the uncontracted to the contracted state may be thus enumerated—

1. Change of form.
2. Development of tension.
3. Change in excitability.
4. Chemical changes.
5. Electrical changes.
6. Thermal change.

We now have to consider each of these in turn, pointing out how the information gained leads us to an understanding of the nature of contraction.

1. The Change in Form

When a muscle such as the frog's gastrocnemius is connected with recording apparatus and is stimulated by means of a single induction shock applied to its nerve, the mechanical result consists of three parts—the latent period, the period of contraction, and the period of relaxation. The latent period is due partly to the inertia of the apparatus, partly to the time occupied in the transmission of the impulse along the nerve and across the nerve ending. But when these have been discounted there remains an interval of time, estimated at $\cdot 0025$ sec., during which changes preparatory to contraction are taking place in the muscle itself. This is known as the **true latent period**.

The period of contraction occupies about $\frac{4}{100}$ sec., and the period of relaxation slightly longer—about $\frac{5}{100}$ sec. It is important to realise that the curve of contraction obtained in this way is but a caricature of the actual change in form, so great is the distortion caused by the inertia of the recording apparatus.

Factors Modifying the Change in Form

1. *Temperature*.—On raising the temperature all three constituents of the curve—latent period, upstroke and downstroke—are shortened. As commonly recorded there is, in addition, an increase in the height of the curve. This, however, can be shown by means of an arrested lever to be instrumental in origin. Alterations in temperature therefore, do not influence the height of contraction.

2. *Load*.—Beginning with a very light weight, increase in the load is at first a stimulus to increased contraction. Beyond a certain weight any further addition leads to a diminution in the height to which it is lifted. There is thus for every muscle a certain load which stimulates it to the maximum work—work being the product of the weight and the height to which the weight is raised.

3. *Strength of Stimulus*.—In the ordinary gastrocnemius

preparation the height of contraction varies with the strength of stimulus. Herein lies an apparent difference between the behaviour of skeletal and of cardiac muscle, for the latter, if it responds at all, responds with the maximum contraction of which it is capable under the circumstances—the **all-or-none principle**. In the striated muscle which we are considering, a submaximal response might conceivably be due either to the stimulation of some of the fibres and not others, those which respond doing so with a maximum contraction, or to the stimulation of all the fibres to an equal but incomplete contraction. Keith Lucas, using a muscle composed of very few fibres, showed that on increasing the stimulus, the increase in response took place in a number of stages *never greater* than the number of fibres. The increased contraction at each stage therefore appeared to be due to the implication of an increasing number of fibres. It would seem, therefore, that a striated muscle fibre obeys the *all-or-none* principle. This feature of muscular contraction is more obvious in the heart, because here all the fibres are knit together, the contraction wave being conducted from one to the other. The difference may be expressed in this way. Cardiac muscle as a whole obeys the all-or-none principle because the individual fibres do so, and any contraction involves all the fibres. Striated *muscle-fibres* also obey the all-or-none principle, but the muscles into which they are bound do not do so, because a variable number of fibres may contract, there being no cell-to-cell propagation of the contracted state.

4. *Frequency of Stimulation : Tetanus*.—When a second stimulus is thrown in before the contraction from a previous stimulus has subsided, a second contraction occurs which begins at whatever stage of contraction the muscle is in as the result of the first, the height of the second contraction being greatest if the second stimulus acts at the summit of the first contraction. This phenomenon is known as **Summation**.

With each succeeding stimulus the height of contraction continues to increase, but the increase becomes progressively diminished until a constant level is reached. As the interval between the stimuli is diminished, the individual curves become more completely fused until all distinction between them is lost. This is known as **tetanus**.

The question now arises whether a *sustained voluntary contraction* is due to the reception by the muscle of a series of interrupted stimuli from the central nervous system, or to some kind of constant stimulus which we cannot imitate experimentally. If non-polarisable electrodes be placed on the forearm and connected with a string galvanometer, on contraction of the flexor muscles the instrument will show a response at the rate of about 50 per second. Voluntary contraction is therefore a form of tetanus, and is due to the arrival of frequently repeated stimuli from the spinal cord.

The Constant Current.—When a muscle is stimulated with the constant current, a single contraction occurs at make of the current and to a lesser extent at break. During the passage of the current there is usually no contraction. Change in the current, then, and not the current itself, is the effective stimulus. We shall study this more closely in the case of nerve.

2. The Development of Tension

Paradoxical as it may seem, shortening is not an essential part of muscular contraction. When a muscle is made to pull against a weak spring the tension of which is approximately constant whatever its length, the contraction is said to be **isotonic**. Under these circumstances the muscle undergoes its maximum shortening, and energy is liberated in the form of work and heat. But if the muscle be made to pull against a strong spring practically no shortening will occur. Yet the muscle has undergone a profound change of state—it *has developed tension*. This is known as an **isometric contraction**. The difference between the

relaxed muscle and the muscle contracted isometrically has been aptly compared with the difference between a *stretched* spiral of lead and a *stretched* spiral of steel. Since practically no work is done in an isometric contraction all the energy liberated appears in the form of heat.

As an example of an isometric contraction which occurs physiologically we may take the contraction of the ventricle before this chamber has begun to empty its contents into the aorta.

3. The Change in Excitability

When a muscle has been stimulated to contraction there occurs an interval of time during which it is incapable of responding to a second stimulus. This is known as **the refractory period**. In skeletal muscle the refractory period is of shorter duration than the time occupied by a single contraction. It is therefore too short to prevent the fusion of repeated contractions into tetanus. In the case of cardiac and unstriated muscle, on the other hand, the refractory period ~~outlasts~~ contraction and relaxation combined. It is upon the great length of the refractory period in these types of muscle that the capacity for rhythmic contraction depends, fusion into tetanus being impossible.

4. The Chemical Changes Accompanying Contraction

Dextrose fed to a beating heart disappears, but whether it is oxidised or converted into glycogen we have no direct evidence. Indirect evidence pointing to oxidation is given by the rise which takes place in the respiratory quotient (see p. 150). That the respiratory quotient is subject to change according to the diet indicates that both fat and carbohydrate can be oxidised.

During contraction there is no increase in protein metabolism. There is a change in the non-protein N. metabolism, but depending upon the form of contraction and the manner in which it is produced. The amount of creatinine and purine bodies has been shown to be increased

as the result of prolonged tonic contraction only. The manner in which carbohydrates are broken down and the significance of lactic acid will be dealt with below.

5. The Electrical Changes

If two non-polarisable electrodes are placed one on the

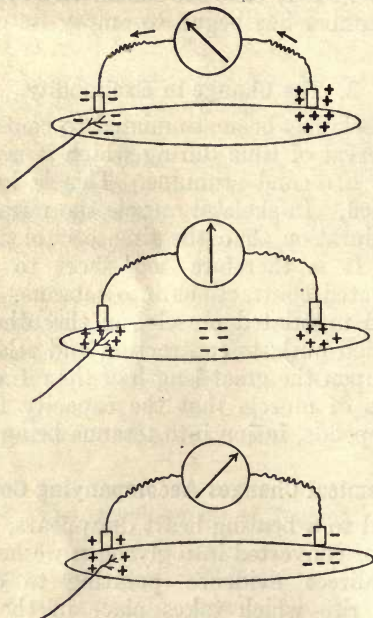


FIG. 5.—Showing three stages in the diphasic variation.

surface, the other on the cut end of a muscle and connected with a galvanometer, the instrument shows a current passing from the intact surface through the galvanometer to the cut surface; the injured part, that is to say, is electro-negative to any other part. This electrical effect is produced even by the injury involved in the most careful

dissection—a fact which led Du Bois-Raymond to regard it as a phenomenon not dependent upon injury, but a property of uninjured resting muscle. Hence the name “current

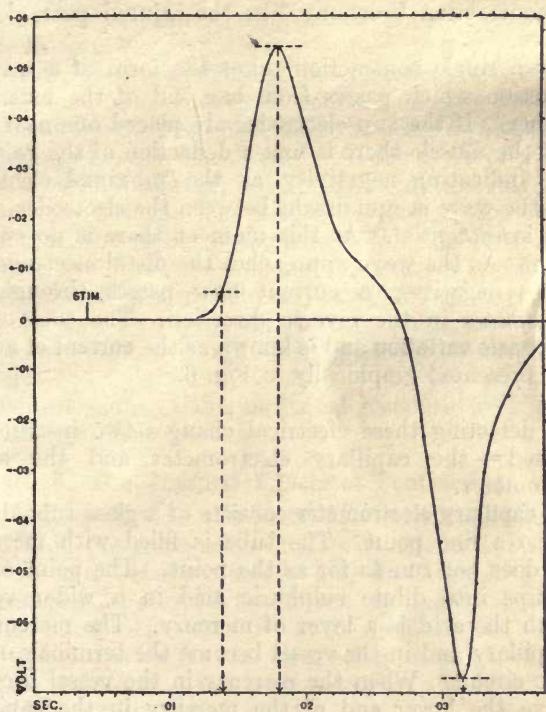


FIG. 6.—Diphasic variation in frog's sartorius (Keith Lucas, from *The Journal of Physiology*).

of rest” by which it was called. From Hermann, however, came the demonstration that in the intact resting muscle, and also in the dead muscle, the muscle is at the same potential throughout, but that when a part of the muscle is

injured a difference of potential is set up between the healthy and the injured part.

A similar difference of potential exists between uncontracted and contracted parts of a muscle, the part which is in contraction becoming, like the injured part, electro-negative.

Now a single contraction takes the form of a wave of contraction which passes from one end of the muscle to the other. If the two electrodes are placed one near each end of the muscle there is first a deflection of the galvanometer, indicating negativity at the proximal electrode. When the wave is equidistant between the electrodes, these are at iso-potential. At this moment there is no current flowing. As the wave approaches the distal electrode this becomes negative; a current now passes through the galvanometer in the reverse direction. The total effect is a **diphasic variation** and is known as the **current of action**. It is represented graphically in Fig. 6.

For detecting these electrical changes two instruments are used — the capillary electrometer and the string galvanometer.

The **capillary electrometer** consists of a glass tube drawn out into a fine point. The tube is filled with mercury which does not run as far as the point. The point of the tube dips into dilute sulphuric acid in a wider vessel. Beneath the acid is a layer of mercury. The mercury in the capillary and in the vessel become the terminals of the electric circuit. When the mercury in the vessel becomes negative the lower end of the mercury in the capillary moves downwards, and vice versa. The movements of the mercury are recorded photographically.

In the **string galvanometer** a fine quartz fibre is suspended in the field of a powerful electro-magnet. When a current passes along the string the latter is deflected to one side or the other according to the direction of the current. Opposite the middle of the string a hole is bored through the

magnet. A powerful beam of light is passed through this hole and the movement of the shadow of the string photographed on a moving plate.

What is the relation between the electrical effect and the change in form?

The rate of propagation of the electrical wave is the same as that of the wave of contraction, any condition which modifies the one, modifying the other in like degree. But whereas a wave of contraction is always accompanied by the electrical change, it is possible to have the latter without the former. The electrical change, too, occurs earlier than the mechanical change. During contraction, therefore, two waves pass along the muscle, an electrical wave followed by a mechanical wave, the electrical wave being the sign of a molecular change preparatory to the mechanical wave, though the latter wave itself may miscarry.

The importance of this electrical response we shall see in connection with the heart.

6. The Thermal Effects of Contraction

We have seen that the process of contraction consists primarily in the assumption of a state of tension, and that this state once attained, energy may be liberated as work if the muscle be allowed to shorten, as heat if shortening be prevented. In warm-blooded animals the energy which appears as heat, so far from being wasted, is the chief factor in maintaining the temperature of the body above that of the environment.

Since in isometric contraction the energy of tension is all converted into one form—heat, we can by measuring the heat evolved estimate the energy of tension.

For detecting the small elevation in temperature which occurs two methods are employed—the thermopile or thermo-electric couple, and the alteration in electrical resistance of a copper wire.

The former method depends upon the fact that if a circuit be formed of two different metals, any difference of temperature between the two junctions will cause a current to pass through the circuit. One junction is placed upon the muscle which is to undergo contraction, the other upon a muscle which remains inactive. The current is detected by a galvanometer.

The bearing of the results obtained by these methods upon the mechanical efficiency of muscle and upon the nature of muscular contraction will be dealt with later. For the moment it is only necessary to state the important fact that *the energy of tension varies directly with the length of the muscle before it contracts.*

THE NATURE OF CONTRACTION

Since all tissue activity is the result of oxidation, we may study the effect of oxygen upon contraction. In the presence of oxygen there is a utilisation of carbohydrate and of oxygen, and evolution of CO_2 . In absence of oxygen, contraction occurs as before and carbohydrate is utilised, but the outstanding chemical change is *the accumulation of lactic acid*. There is no evolution of CO_2 other than can be explained as produced secondarily by the action of the lactic acid upon the bicarbonates present.

Under these conditions, however, the muscle soon becomes fatigued, recovery ensuing on the administration of oxygen.

Oxygen therefore, while essential for the continued activity and well-being of the muscle, is not necessary for the actual contractile process. Nor is anaerobic contraction, due to the consumption of a kind of intramuscular store of oxygen, otherwise there would be a considerable evolution of CO_2 . The act of contraction, therefore, is associated chemically not with an oxidative process but with the formation of lactic acid. The uncontracted muscle contains within it a store of potential energy which in the assumption of the contracted state is capable of transforma-

tion into work or heat, and the part played by oxygen lies not in effecting this transformation of energy but in the restoration of the condition of high potential. What is the nature of the oxidation involved in the secondary process of restoring the muscle to the state of high potential?

In this process there is no disappearance of sugar, whereas carbohydrate does disappear in the act of contraction both in the presence and in the absence of oxygen, lactic acid appearing in the latter case but not in the former. The conclusion is therefore drawn that the energy for the recuperation of muscle into its high potential state is derived from the oxidation of lactic acid formed in the act of contraction.

Can it be shown that the energy thus obtained from the oxidation of lactic acid is sufficient? One gram of acid on oxidation gives out 3,700 calories, whereas in the process of recovery the utilisation of the same amount of acid corresponds to the production of only 450 calories. The source of energy, therefore, is amply sufficient.

Returning now to the process of contraction, if this is not produced chemically by oxidation, as in the case of an internal combustion engine, to what is it due? It cannot be due to the conversion of carbohydrates into lactic acid, for this reaction is practically isothermic. There are, indeed, strong reasons against its being a chemical reaction at all. The mechanical efficiency of the process has been estimated at practically 100 per cent., a degree of efficiency which is not approached by any known form of chemical energy.

If the energy appears not to be chemical there is some evidence to indicate that it is physical. We have seen in discussing isometric contractions that although there is practically no deformation, there is a very profound change—a change of tension. The degree of tension developed, and therefore of heat evolved, is greater in an isometric than in an isotonic contraction, and varies directly, not with the volume, but *with the length of the fibres*, that is to

say, with the area of longitudinal surfaces within the muscle. This indicates that contraction is dependent upon change in tension between two surfaces, probably between sarcostyles and sarcoplasm. The development of lactic acid may be the factor determining the change of tension.

But surface tension is not the only property influenced by contraction. A fatigued muscle has a higher osmotic pressure than resting muscle. Upon this fact is based a theory which attributes contraction to an aggregation of colloid particles, with consequent liberation of electrolytes. The increased concentration of these causes, by osmosis, a flow of water in a particular direction.

We may thus sum up what we have said above. Muscular activity consists of two alternating phases: (1) *A phase of contraction* which, though associated with the formation of lactic acid, is essentially a physical process involving surface and osmotic phenomena. No gaseous metabolism is involved. (2) *A phase of recovery* consisting in the restoration of a state of high potential. It is in this phase that oxygen is used.

The Mechanical Efficiency of Contraction

It has been found that the energy of tension may have an efficiency of 100 per cent. But in the phase of recovery an amount of heat is produced equal to that produced in the phase of contraction. This reduces the efficiency of the whole contractile process to 50 per cent. In sustained contraction, or tetanus, the efficiency becomes very much diminished; the form of contraction is therefore an important factor. The average efficiency of contraction has been estimated at about 25 per cent.

CHAPTER V

THE HEART

THE NATURE OF THE HEART-BEAT

INVESTIGATION into the nature of the heart-beat may be said to have been inaugurated in 1852 with the experiments of Stannius upon the frog's heart. Previous to this, all that was known with certainty was that the beat was independent both of connection with the central nervous system, and of the presence of blood in the cavities. Stannius found that when a ligature was tied at the junction of the sinus and auricle (**Stannius's First Ligature**) the sinus continued to beat while the auricle and ventricle stopped. This he attributed to paralysis of Remak's ganglion situated at the site of the ligature. On applying a ligature between the auricle and ventricle (**Stannius's Second Ligature**) he found that while the auricle remained quiescent, the ventricle resumed beating. This he considered to be due to a stimulation of Bidder's ganglion situated at the junction of these two chambers. Stannius's experiment, therefore, seemed to confirm the view already held that the cause of the beat lay in the activity of the nerve-cells embedded in the heart-wall.

In 1881, the accuracy of these experiments and the interpretation put upon them by Stannius were called in question by Gaskell. Gaskell drew attention to the fact that the stoppage of auricle and ventricle following the first ligature was only temporary, and was soon followed by the development of rhythmic contraction of these chambers slower than and independent of the contraction

of the sinus. Stannius had observed this, but had paid no attention to it. Gaskell further found that if the second ligature were replaced by slow compression of the auriculo-ventricular junction the ventricle first stopped beating, but afterwards began to beat with a rhythm slower again than that of the auricle. Gaskell was therefore led to the view that the origin of the beat was to be found in the inherent property of rhythmicity possessed by the heart-muscle. In other words, he founded the *Myogenic Theory* of the Heart-beat.

In confirmation of this view came the later observations that the heart of the developing chick begins to beat before any nerves have migrated into it, and that the separated apex of the frog's ventricle, demonstrably free from nerves, continues to beat if properly nourished.

Rhythmic contraction then, being a property of heart-muscle, what is the cause of the conduction of the beat from the sinus to the ventricle? Gaskell proved that the conduction of the beat was muscular by two experiments performed on the heart of the tortoise. In this animal sinus and ventricle are connected together by a band of auricular tissue. When a series of interdigitating cuts is made into the band the conduction of the beat is unaffected. This would not be the case if the conduction were due to nerves. Again, if this band is little by little cut almost completely across (Fig. 7), a stage is reached when the part of the auricle distal to the cut responds only to every alternate beat of the proximal part. On cutting further, it responds only to every third beat, and so on until eventually the bridge of tissue becomes so much narrowed that no wave can pass along it. The distal part then develops a rhythm of its own. Clearly, therefore, conduction is dependent upon and due to the integrity of the muscle itself.

Both the origin and the conduction of the beat being myogenic, why does the beat travel from sinus to ventricle and not in any other direction? Gaskell showed that this was due to a greater rhythmicity possessed by the sinus.

When all three chambers are beating independently, the rhythm is quickest at the sinus, slowest at the ventricle, and intermediate at the auricle. Normally therefore, the inherent rhythm of the auricle and ventricle is not called into play, for its effect is anticipated by contraction of these chambers, due to the arrival of a wave from the sinus. The auricle and ventricle, therefore, contract at

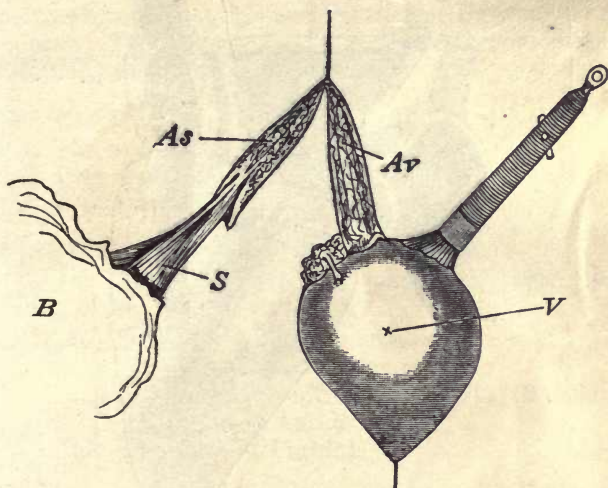


FIG. 7.—Heart of tortoise prepared to show partial heart-block. The auricular tissue is cut between *As* and *Av* (Gaskell).

the rate set by the sinus. For this reason the sinus is called the **pace-maker** of the heart. To confirm this view, Gaskell cooled the sinus and warmed the ventricle. By so doing he lowered the rhythmicity of the former and raised the rhythmicity of the latter. The result was that the beat passed from ventricle to sinus. The progression of the beat is therefore due to the fact that different parts of the heart possess different degrees of rhythmicity.

It will be noticed that the rhythmicity is greatest in that

part of the heart which has the feeblest contraction, and is least in that part where contraction is strongest. Here then is a partial differentiation of the two fundamental properties of heart-muscle—rhythmicity and contractility.

It now remains to us to show how far this explanation of the nature of the heart-beat is applicable to the more

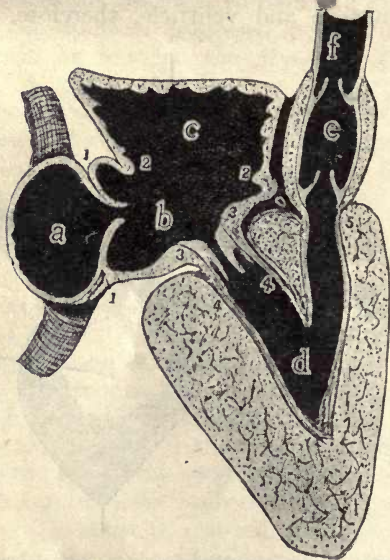


FIG. 8.—A generalised type of vertebrate heart (Keith). a, sinus venosus; b, sino-auricular canal; c, auricle; d, ventricle; e, bulbus cordis; f, aorta.

complicated heart of the mammal. A generalised form of primitive vertebrate heart is shown in Fig. 8. It is composed of four serial chambers: (a) the sinus, (b) the auricular canal, part of which is invaginated into (d) the ventricle, (e) the bulbus cordis. The auricle is a lateral diverticulum of the auricular canal. The sinus and auricular canal may be regarded as forming the rhythmic, the auricle and ventricle the contractile parts.

This differentiation in function is associated with a differentiation in structure, the rhythmic fibres retaining their embryonic form and circular disposition, the contractile fibres undergoing an approximation to the skeletal form in developing a partial cross-striation.

As this type of heart develops into the mammalian form, the sinus and auricular canal become lost as separate chambers, and their tissues are submerged by the great hypertrophy of the auricle and ventricle. But they do not disappear. They persist, retaining their embryonic nature, and forming the following structures—

Developed from the Sinus.

1. The sino-auricular node.¹
2. Part of the interauricular septum.
3. The opening of the coronary sinus.

Developed from the Sino-auricular Canal.

4. The auriculo-ventricular junctional tissue, consisting of—

- (a) Fibres from the auricular septum to
- (b) The auriculo-ventricular node.
- (c) The auriculo-ventricular bundle (**Bundle of His**) and its two branches.
- (d) The fibres of Purkinje.

So important to the modern conception of the heart-beat has been the discovery of these remnants that it is necessary to describe their anatomical disposition, and to show how they differ structurally from the ordinary heart-muscle.

Disposition and Structure of the Junctional Tissue

The ordinary cardiac muscle is composed of columns of short cylindrical fibres, united irregularly to those of

¹ The sino-auricular node of the mammalian heart must not be confused with the sino-auricular canal of the primitive vertebrate heart.

adjacent columns. Cross striation is present, but not to the same degree as in skeletal fibres. The single nucleus is centrally situated. Longitudinal fibres appear not only in the individual cells, but also traversing the partitions between them.

The **sino-auricular node**, 2 mm. in thickness, begins at

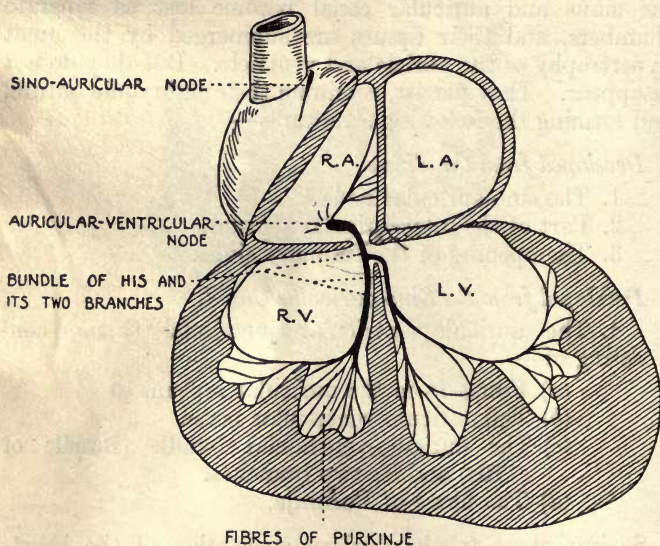


FIG. 9.—Diagrammatic coronal section of the heart to show the junctional tissue. The position of the sino-auricular node is shown on the surface.

the junction of the superior vena cava and the right auricle, and extends about 2 cm. along the sulcus terminalis. The cells are fusiform, striated, and plentifully surrounded by connective tissue. They are in intimate association with nerve-fibres and nerve-cells, through which connections can be traced with the vagus and sympathetic.

The auriculo-ventricular junctional tissue begins in the form of fibres from the region of the coronary sinus, and

from the inter-auricular septum. These converge upon the **auriculo-ventricular node**, a mass of tissue lying on the right border of the septum in the neighbourhood of the coronary sinus. From this node emerges the **auriculo-ventricular bundle**, which passes forward, still on the right side, to the central fibrous body of the heart. At the anterior end of the *pars membranacea* of the interventricular septum, it divides into two branches, the **right branch** passing immediately beneath the endocardium to the papillary muscles, where it arborises. The **left branch**, after piercing the *pars membranacea*, proceeds downwards along the left side of the septum, where it arborises. The extensive arborisations on both sides are known as the **Purkinje fibres**. These, ramifying in the subendocardial tissue, eventually terminate by becoming continuous with the ventricular substance, and in particular with the papillary muscles.

It is important to realise that throughout its course the fibres of the junctional system are surrounded by connective tissue which isolates them from the main ventricular mass until their termination is reached.

At the auriculo-ventricular bundle, the fibres resemble those of the sino-auricular node in their shape, and in their isolation by connective tissue. But as they are traced downwards, the cells come to have a less plexiform, more parallel disposition, they become paler and larger, the nucleus is multiple, and the striation is confined to the periphery of the cells.

Chemically, the junctional tissue differs from the contractile in containing a high percentage of glycogen.

The auriculo-ventricular bundle forms the only connection, other than fibrous, between auricles and ventricles.

The Function of the Junctional Tissue

The Sino-auricular Node is the Pace-maker of the Heart

We have seen that when a wave of contraction passes along a muscle, the part which is in contraction is electro-

negative to the rest of the muscle. The part which is the earliest to become electro-negative is therefore the part which is earliest to contract. Lewis, by systematically exploring the auricle, placing the electrodes on various points, found that the region which first becomes negative is the sino-auricular node.

Not only is the sino-auricular node the site of origin of the impulse, but it is the part most sensitive to local influences. Cooling slows the rhythm only when applied here. It is clear, therefore, that the sino-auricular node plays the same part in the mammalian heart as the sinus, from which the node is derived, plays in the amphibian organ.

The Auriculo-Ventricular Bundle

It is now proved that the proper conduction of the impulse from the auricle to the ventricle is dependent upon the integrity of this structure. When the bundle is injured the following effects are produced according to the degree of the injury.

1. Prolongation of the interval between the auricular and ventricular contractions.
2. An occasional ventricular lapse.
3. Response of the ventricle only to alternate or to every third auricular beat. (**Partial Heart-block.**)
4. Complete failure of conduction from auricle to ventricle, the latter chamber beating independently. (**Complete Heart-block.**)

The same changes occur when the bundle is diseased, the condition being known as Stokes-Adams' disease.

It will be seen that the effects produced by injury to the bundle are the exact counterpart of those obtained in Gaskell's experiment upon the heart of the tortoise. The bundle performs the same function as the sino-auricular canal from which it is developed.

THE CARDIAC CYCLE

Intracardiac Pressure

When the heart is beating at its normal rate—72 beats per minute—the complete cycle of changes occupies about 0·8 sec. and consists of three phases—

Auricular systole	0·1 sec.
Ventricular systole	0·3 sec.
Diastole	0·4 sec.

The pressure changes occurring in the heart during the cycle have been investigated by the direct introduction

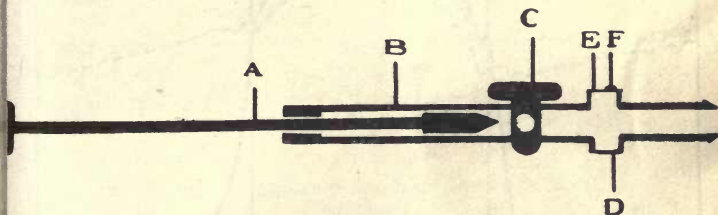


FIG. 10.—Piper's manometer (from Starling's *Principles of Physiology*).

into the chambers of specially-constructed manometers. Of the many forms of these which have been invented, the one which most effectively eliminates instrumental error is *Piper's* (Fig. 10). It consists of a cannula B, fitted with a trocar A. At one side of the cannula, at E, is an elastic membrane, upon which is fixed a mirror F. C is a tap which when open admits the passage of the trocar. The manometer is inserted direct into the desired chamber of the heart, the point of the trocar piercing through the wall. The trocar is then withdrawn and C closed. Changes in pressure in the chamber cause alternate stretching and slackening of the membrane, these movements being recorded in a magnified form by light thrown on the mirror. The results obtained when manometers are thrust

simultaneously into the auricle, ventricle and aorta are shown diagrammatically in Fig. 11.

Systole begins with a slight rise of pressure (at 1) in the auricle due to contraction of this chamber. Immediately afterwards the ventricular pressure rises, slowly at first, then more rapidly. As it rises, there occurs (at 2) a second

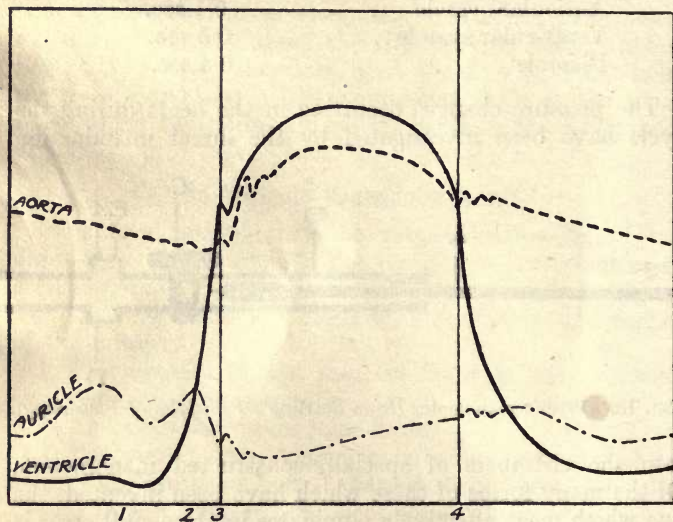


FIG. 11.—Changes in pressure during a complete heart-beat in the left auricle, left ventricle, and aorta (modified from Piper).

rise in the auricular pressure brought about by the sudden closure of the auriculo-ventricular or mitral valve. At 3, the ventricular pressure is sufficient to force open the aortic valve. As the blood flows into the aorta the ventricular pressure describes a rounded summit known as the systolic plateau. This terminates in a sharp fall of pressure, at the middle of which the aortic valve closes, the point of closure being marked by the secondary rise

(at 4) of the aortic pressure, due to the rebound of the aortic blood from the closed valve. During the early part of the fall in ventricular pressure, the auricular pressure undergoes a third rise attributed to gradual filling.

The Venous Pulse

Measurement of the intracardiac pressure is a means of finding out what the several chambers are doing, but it is a means which from its nature can only be used upon animals. We have no method of discovering the intracardiac pressure in the human subject, but we can trace to some extent the changes which are occurring in the right auricle.

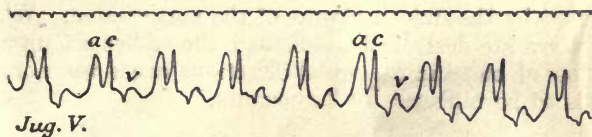


FIG. 12.—Tracing of jugular pulse (from Starling's *Principles of Physiology*).

When a tambour is pressed on the right side of the neck opposite the jugular vein, and the movement transmitted to recording apparatus, each beat is found to be accompanied by three waves, known as the *a*, *c*, and *v* waves. These are shown in Fig. 12. The *a* wave occurs immediately after the first auricular wave, and is an expression of the rise in auricular pressure which is produced either by the holding up of the blood in the auricle, or by the regurgitation of some of the blood into the vein, the superior vena cava having no valve. The *c* wave coincides with the zenith of ventricular and aortic pressure. It depends upon and is a measure of the ventricular contraction. It is produced either by the transmission of the impulse from the carotid artery through the tissues of the neck or by the closure of the auriculo-ventricular valve. The *v* wave is

usually attributed, like the third auricular wave, to the gradual filling of the auricle, the auriculo-ventricular valve being closed.

The *a* wave is therefore an index of auricular, and the *c* wave an index of ventricular contraction, while the distance between them is a measure of the rate of conduction from the auricle to the ventricle.

The Heart-Sounds

At each beat two sounds are normally heard. The first is best heard at the apex and is due to the contraction of the ventricles and to the closure of the mitral valve. The second sound, shorter and sharper than the first, is also audible at the apex, but is heard best at the base. It is caused by the sudden closure of the aortic valve. When the valves are destroyed by disease, the eddies set up and the flow of blood in abnormal directions cause the normal sounds to be replaced by "murmurs."

Electrical Changes in the Heart

The apparatus used for the detection of the current of action of the heart *in situ* is an adaptation of the string galvanometer—known as the electro-cardiograph (see p. 44). Owing to the saline content of the tissues and tissue-fluids, the body conducts an electric current as though it consisted merely of salt solution. When a difference of potential occurs anywhere within the body, as in the heart, this can by appropriate means be detected at the surface. Owing to the oblique disposition of the heart, a potential at the base tends to spread upwards and to the right, a potential at the apex downwards and to the left. The subject is put into circuit with the galvanometer by having his right hand and left foot inserted into pots containing salt solution wired up with the two ends of the string. The axis of the heart is then more or less in line with the circuit, and any difference of potential between base and apex of the heart is recorded by the string.

It is conventional to take the records in such a manner that negativity at the base is shown on the photographic record by a deflection upwards.

An electrocardiogram thus obtained is shown in Fig. 13. It will be seen to differ considerably from the simple diphasic variation of skeletal muscle. There are two reasons for this discrepancy. First, the right hand and left foot do not accurately represent the base and apex of the heart respectively; secondly, the heart is far from being a simple muscle.

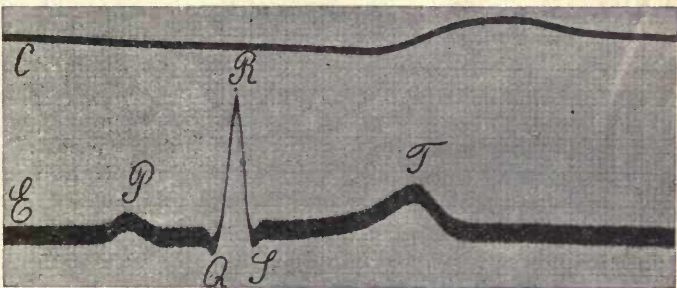


FIG. 13.—Human electrocardiogram (from Starling's *Principles of Physiology*).

The record usually consists of five waves, to which are given the conventional names, P, Q, R, S, and T. Of these three, P, Q, and T indicate base-negative currents; the remaining two, Q and S, base-positive.

The interpretation of the electrocardiogram is a matter of considerable difficulty. The wave P is admittedly of auricular origin. During the iso-electric period following it, neither auricle nor ventricle is contracting, the impulse passing from the one to the other along the auriculo-ventricular bundle. Q is of inconstant recurrence and uncertain origin. R, which is always the most striking feature of the electrocardiogram, indicates contraction at

the base of the ventricles. S is due to contraction at the apex. Then follows a prolonged iso-electric period which is succeeded by the slow base-negative wave T. As to the nature of this last wave, there is much uncertainty. It may be due to the ventricular contraction ending at the base, at the opening of the aorta.

THE WORK OF THE HEART

The aorta and large arteries may be said to form a reservoir at high pressure from which blood is supplied to the various tissues. The needs of the tissues for blood are constantly fluctuating according to physiological activity. We shall see how in the different tissues the supply is made to meet the demands. It is only necessary to say here that the fluctuation is greatest in the abdomen and limbs, least in the brain. It follows that if there were no compensating mechanism, the arterial blood-pressure would vary as the flood-gates into the tissues—for instance, the muscles—were open or shut, and the brain would be exposed indirectly to a diminution in its blood-supply at the very time when this organ would need blood most for the increased cerebral activity which accompanies physical exertion. But in the intact animal when the arterial reservoir is being drained abnormally rapidly the pressure within it, so far from falling, actually rises. There exists, therefore, a mechanism which seems to have for its object the proper nourishment of the brain under all circumstances.

In whatever this mechanism may be found to consist, it must involve ultimately a variation in the output of the heart, since it is only by an alteration in the amount of blood which enters the arterial reservoir that the pressure here can be maintained constant in the face of alterations in the rate at which blood leaves the reservoir.

The work done by the heart may therefore be said to consist in the maintenance of a constant or nearly constant arterial pressure. From a mechanical point of view, this

work consists in raising the blood from a region of low to a region of high pressure, and in imparting to the same blood a certain velocity. The work performed by the left side of the heart, at each beat, is expressed approximately by the formula—

$$W = QR + \frac{wV_2}{2g}$$

where W is the work, Q the quantity of blood driven out at each beat, R the average arterial resistance, w the mass of blood moved, V its velocity immediately after it has been discharged, and g the acceleration due to gravity. A similar formula gives the work done by the right side, the only factor which is different being R .

On the basis of this formula, the work done by the resting heart at each beat has been estimated at 100 grammeters per beat, or about 7,200 grammeters per minute. During exercise, this figure is greatly increased owing to the increased output, the increased arterial pressure, and the increased velocity imparted to the blood.

For measuring the output of the ventricle at each beat in the intact animal, only indirect methods are available. One of these is **Zuntz's Method**.

Two data are necessary—

1. The amount of oxygen leaving the lung in a given time.
2. The difference in the oxygen content of arterial and venous blood. In the case of a horse, it was found that the arterial blood contained 10.33 per cent. more oxygen than venous blood, or in other words that 100 c.c. of blood in passing through the lungs had absorbed 10.33 c.c. of oxygen. Since 2732 c.c. of oxygen was absorbed from the lungs in one minute, the amount of blood which flowed through the lungs in that period was—

$$\frac{100 \times 2732}{10.33} = 26.457 \text{ litres.}$$

Arguing from a comparison of the body-weight it is estimated that in man the average output of each ventricle per beat at rest is 60 c.c.

The same figure has been arrived at by another method due to Krogh. This method is applicable to man. The subject breathes a certain volume of nitrous oxide and an estimation is made of the amount which is absorbed in a certain time. The rate of absorption of the gas at the same pressure as it exists in the lungs is then determined *in vitro*. From this is calculated the volume of the blood passing through the lungs in a given time.

ADAPTATION OF THE HEART

It is estimated that the output of the heart per minute varies from 3 litres during rest to 21 litres during violent exercise. The heart therefore has a very considerable power of responding to the demands made upon it. Variations in the output can be brought about in two ways—

1. By an increase in the rate of the beat, and
2. By an increase in the output per beat; that is to say, by alteration in the capacity of the heart at each diastole.

In considering how the heart thus adapts itself it will be most convenient to inquire first how far the capacity for adaptation is inherent to the heart itself, and expresses itself independently of nervous connections, and secondly how this inherent tendency, if it exists, is modified or supplemented by the agency of the central nervous system.

The Isolated Heart

The behaviour of the heart when freed from its nervous connections is best studied by means of the *heart-lung preparation* invented by Starling. Here is Starling's description of the apparatus.

“Artificial respiration being maintained, the chest is opened under an anæsthetic. The arteries coming from the arch of the aorta—in the cat, the innominate and the left subclavian—are

then ligatured, thus cutting off the whole blood-supply to the brain, so that the anæsthetic can be discontinued. Cannulæ are placed in the innominate artery and the superior vena cava. The cannulæ are filled beforehand with a solution of hirudin in normal salt solution, so as to prevent clotting of the blood during the experiment. The descending aorta is closed by a ligature. The

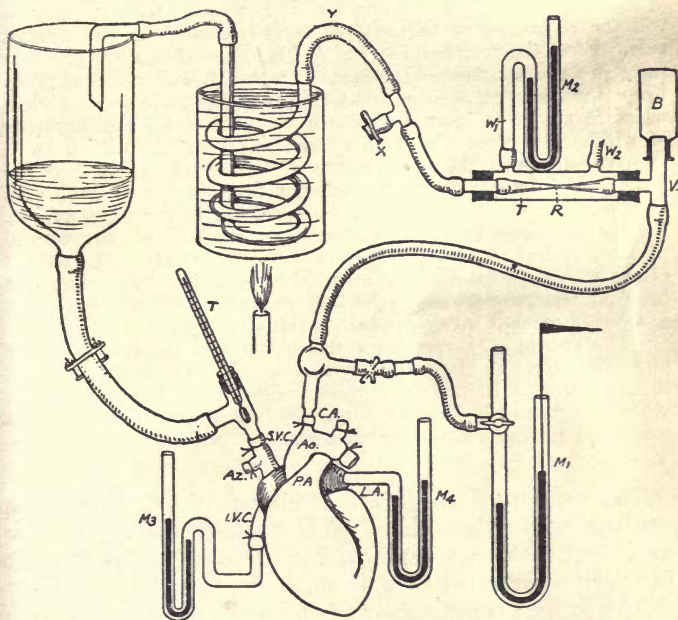


FIG. 14.—The heart-lung preparation. (From *The Journal of Physiology*.)

only path left for the blood is by the ascending aorta, and the cannula CA in the innominate artery. The arterial cannula communicates by a T-tube with a mercurial manometer M^1 to record the mean arterial pressure, and passes to another T-tube v one limb of which projects into the test-tube B. The air in this test-tube will be compressed with a rise of pressure, and will serve as a driving force for the blood through the resistance. It thus takes the part of the resilient arterial wall. The other limb of the test-

tube passes to a resistance R . This consists of a thin-walled tube (e. g. a rubber finger-stall) which passes through a wide glass tube provided with two lateral tubulures w_1, w_2 . One of these is connected with a mercurial manometer, M_2 , and the other with an air reservoir into which air can be pumped. When air is injected into the outer tube, the tube R collapses, and will remain collapsed until the pressure of the blood within it is equal or superior to the pressure in the air surrounding it. It is thus possible to vary at will the resistance to the outflow of the blood from the arterial side. From the peripheral end of R , blood passes at a low pressure through a spiral immersed in warm water, into a large glass reservoir. From the reservoir a wide india-rubber tube leads to a cannula which is placed in the superior vena cava, SVC , all the branches of which have been tied. This cannula is provided with a thermometer to show the temperature of the blood supplied to the heart. A tube placed in the inferior vena cava and connected with a water manometer shows the pressure in the right auricle. On the recording surface we thus have a record of the arterial pressure and of the pressure within the right auricle. The output of the whole system can be measured at any time by opening the tube X , clamping Y , and allowing the blood to flow for a given number of seconds into a graduated cylinder. . . .

"The output . . . represents the ventricular output minus the blood-flow through the coronary arteries. It is possible, however, to insert a cannula into the coronary sinus, and so to measure the blood-flow through the heart-muscle." Artificial respiration is continued throughout the experiment.

The volume of the heart is measured by means of a cardiometer, a glass vessel which encloses the organ. By a side tube it is connected with a tambour, the movement of which is recorded on a drum.

The oxygen consumption of the heart is estimated from the oxygen absorbed by the lungs.

We may now briefly discuss how the output is affected by changing any of the conditions.

1. *Temperature of the Blood*.—The beat increases in rate with rise of temperature.

2. *Reaction of the Blood*.—At a certain reaction of the blood, the output of the heart is maximum. Slight increase

in H ion concentration diminishes the amplitude of the beat, the rate being unaffected.

3. *Adrenalin*.—Adrenalin, the substance produced by the suprarenal glands, causes an acceleration and augmentation of the beat.

4. *Changes in the Arterial Pressure*.—The effect of changing the arterial pressure is shown in Fig. 15 and in this Table:—

Arterial Pressure.	Systemic output c.c. per min.	Total Coronary output (calculated).	Total output of Left Heart.	Venous Pressure.
84	811	40.80	851.80	9.6–12.4
140	770	70.75	840.75	8.0–11.2
208	600	260.30	860.30	12.0–22.0

It will be seen that the output of the heart and the rate of the beat are unaffected. A glance at Fig. 15 will show that as the arterial pressure rises the volume of the heart increases (downward movement of the cardiometer curve), and that this increase occurs by a slight distension at each beat until the new volume is acquired. Another change is the great increase in the blood-flow through the coronary circulation, associated with a rise in the amount of oxygen used. How these occur is as follows. Suppose the mean arterial pressure is 80 (systolic pressure 100, diastolic 60). Suppose 8 c.c. is the amount of blood expelled at each beat, the ventricle being completely emptied. Blood begins to flow from the ventricle when the pressure in this chamber just exceeds 60, and in order that the ventricle may be completely discharged the pressure within it must finally exceed 100. Suppose that the mean arterial pressure is now artificially raised to 110 (systolic 130, diastolic 90). At the next beat following the change no blood leaves the ventricle until the intraventricular pressure exceeds 90; for the ventricle to be completely discharged, a pressure exceeding 130 is necessary. But systole terminates as before, when

the pressure just exceeds 100, for the heart is, as it were, unprepared for the extra call made upon it. At this beat only a part of the 8 c.c.—let us say 4 c.c.—is discharged.

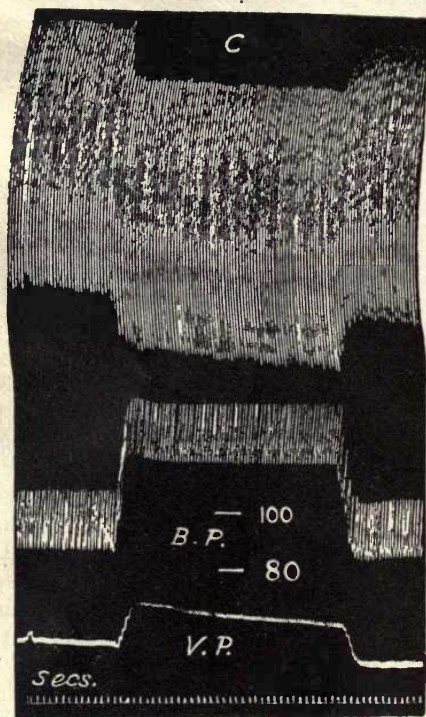


FIG. 15.—The effect of increased arterial pressure on the heart. *C*, cardiometer; *B.P.*, arterial blood pressure; *V.P.*, pressure in inferior vena cava. —100 and —80 indicate height of blood pressure in mm. Hg. (From Starling's *Principles of Physiology*.)

The heart at the end of systole contains 4 c.c. During the subsequent diastole, another 8 c.c. flows in. To accommodate 12 c.c., the volume of the ventricle during diastole is

increased by distension. The next systole is stronger, and results in, say, 6 c.c. being expelled, 6 c.c. remaining in the ventricle. At the next diastole, the distension is greater

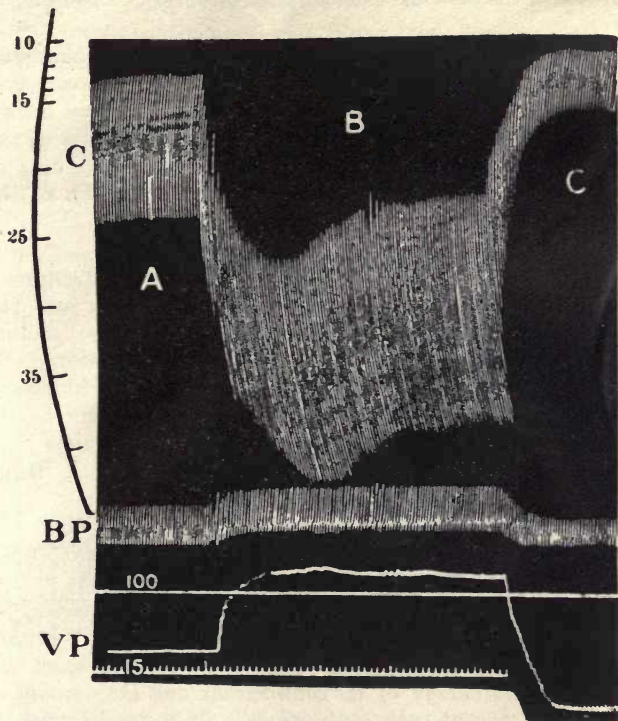


FIG. 16.—Effect of alterations in venous supply on the heart. The curved line on the left shows the ventricular capacity in c.c. (From Starling's *Principles of Physiology*.)

still, 6 c.c. + 8 c.c. = 14 c.c., and is followed by a still stronger systole, which probably succeeds in expelling 8 c.c., leaving 6 c.c. in the ventricle. The normal output is thus restored; the only difference lying in the diastolic

and systolic capacities of the ventricle, which, instead of being 8 c.c. and 0 c.c. respectively, are now 14 c.c., and 6 c.c. *The increased work of the heart is associated with increased distension at diastole and incomplete emptying at systole.*

5. *Changes in the Venous Inflow.*—The result of changing the venous inflow is seen in Fig. 16. It will be seen that rise of venous pressure, like rise of arterial pressure, causes a gradual distension and again no change in the rate of the beat. The difference is that there is now *an increase in the output per beat*, shown in the increased excursion of the cardiometer.

The factors which these two experiments have in common are the increased work performed by the heart, and the increased distension *at diastole*. How are these factors related? The greater energy of contraction cannot be due to the stretching of the fibres owing to increased tension through abnormal filling, for no such increase in tension exists. As the blood flows in, the ventricle wall simply gives, the pressure at the end of diastole being practically nil whatever the capacity of the chamber.

In discussing skeletal muscle we have seen that the energy of contraction varies directly with the initial length of the fibre (p. 46). The same rule applies to the heart, and is the cause of the phenomena we have been discussing. This is called by Starling the **Law of the Heart**. “*Within physiological limits the larger the volume of the heart, the greater are the energy of its contractions and the amount of chemical change at each contraction.*” It must be remembered, however, that with the heart *in situ*, the amount of dilatation which it can undergo is limited by the inextensible pericardium.

The Influence of the Nervous System upon the Heart

Having shown the power of adaptation possessed by the isolated heart, we pass on to consider what further modifica-

tions in the heart's activity occur through the intervention of the central nervous system.

The Efferent Nerves of the Heart

The heart receives efferent fibres from two sources, the vagus and the sympathetic.

The Vagus—

1. Slows the beat and stops it on strong stimulation;
2. Diminishes the amplitude of the beat;
3. Prolongs the auriculo-ventricular interval, by depressing the conductivity of the bundle of His.

The Sympathetic, the fibres of which emerge from the upper thoracic segments of the cord, is in every way antagonistic to the vagus. It therefore—

1. Quickens the beat;
2. Increases its amplitude;
3. Decreases the auriculo-ventricular interval.

The centre for the control of the heart resides in the medulla at the nuclei of origin of the vagus. This region probably controls the spinal centres from which the sympathetic fibres issue.

The efferent nerves may be called into play reflexly by stimulation of sensory nerves, by impulses from the higher centres, and by changes in the blood bathing the centre.

Cardiac Reflexes

Stimulation of almost any sensory nerve has the effect of altering the rate of the beat in one direction or the other. The most important reflexes, however, are those arising in the heart itself and in the lungs.

Reflexes originating in the Heart.—The heart is liberally supplied with afferent fibres, which travel up in the vagus, and probably also in the sympathetic. Arising at the base of the heart, and at the root of the aorta, are the *depressor*

fibres. These in the rabbit form a separate nerve, the *depressor nerve*, in the neck, but in most animals are incorporated throughout with the vagus. On stimulating the central end of the depressor nerve in the rabbit, there occur slowing of the heart and fall of blood-pressure, the former due to impulses travelling down the vagus, the latter to dilatation of the peripheral blood-vessels—chiefly those of the abdomen.

We saw that in the heart-lung preparation, rise in the arterial pressure, though it caused dilatation of the heart with unaltered output, did not affect the frequency. When the arterial pressure is increased in the intact animal, the heart is slowed (**Marey's Law**). The rise in pressure is a stimulus to the depressor nerve-endings. Here then is a protective mechanism whereby the heart is eased of a load which is too great for it.

But the afferent fibres do not all stimulate the vagus centre. We saw that in the isolated heart, the output increased with the venous inflow, but the frequency of the beat was unchanged. There is evidence to show that abnormal distension of the *right auricle* stimulates efferent nerve-endings to produce reflex quickening of the heart.

Reflexes originating in the Lungs.—The beat is quickened during inspiration, and slowed during expiration. This phenomenon, which is known as *sinus arrhythmia*, is abolished when the vagi are cut. In children it occurs with normal breathing; in adults usually only during excessive respiratory movement.

The Influence of the Higher Centres upon the Medulla

Certain mental states, such as strong emotions, affect the cardiac centre directly. The quickening of the beat which occurs at the beginning of exercise is also produced by the direct action upon the medulla of impulses originating in the cerebral centres and called into play by the psychological process of attention.

Influence of the Blood-Supply upon the Cardiac Centre

Rise in the arterial pressure within the skull causes reflex slowing of the heart by stimulating the vagus centre. Increase in the hydrogen ion content of the blood has the same effect.

From what has been said, it is clear that, owing to its being controlled by the central nervous system, the heart possesses a much greater latitude of adaptation than if it were independent. The function of the cardiac centre is to regulate the output of the heart according to the needs of the body as a whole. It must be remembered however that we are here dealing with only one aspect of a complex story. The greatest increase in the activity of the heart occurs as the result of an unusual demand for oxygen by the tissues, and this demand is met not only by a quickening of the circulation but by changes in other systems. Until these have been separately considered, we shall not be in a position to understand fully the significance to the animal economy of the factors affecting the activity of the heart.

CHAPTER VI

THE CIRCULATION OF THE BLOOD

THE SYSTEMIC CIRCULATION

The Velocity of the Blood

WHENEVER an artery divides, the branches, though individually smaller than the parent-trunk, have collectively a larger area of cross-section. The combined area of cross-section of the capillaries is many hundred times greater than that of the aorta. Similarly, as the veins converge, the total area of the tributaries becomes smaller. Blood is therefore flowing away from the heart in a stream which is ever widening, and back to the heart in a stream which is ever narrowing. On this account the velocity of the blood diminishes as it travels along the arteries, reaches its minimum in the capillaries and quickens again in the veins.

We have no means of measuring the velocity of the blood directly in the human subject. An indirect calculation can, however, be made of the rate at which it travels through the aortic orifice. The output of the left ventricle per beat while the body is at rest we have seen to be on an average 60 c.c. At a pulse rate of 72, this gives 4320 c.c. per minute. The area of cross-section of the aorta is 4 sq. cm. In one minute, therefore, a column of 1080 cm. passes along the aorta. Were the flow continuous, this would give a velocity of 18 cm. per sec.

Many instruments have been invented for measuring the velocity of the blood in animals. For use in arteries

a record must be made not only of the average rate of flow but also of the fluctuations due to the heart-beat. One of the simplest instruments for showing this is **Chauveau's hæmadromograph**, a diagram of which is given.

The apparatus is shown in Fig. 17. The horizontal part of the tube is inserted into the cut artery, *c* being attached to the

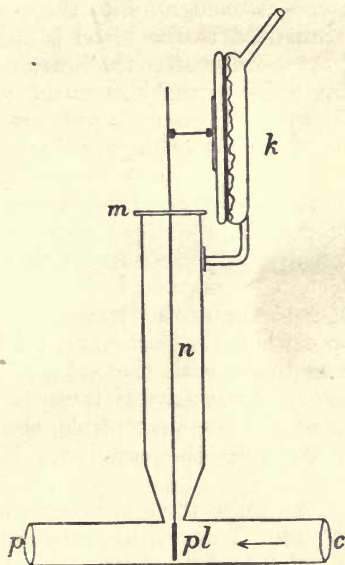


FIG. 17.—Chauveau's hæmadromograph. (From Starling's *Principles of Physiology*.)

central and *p* to the peripheral end. Into the tube is suspended the pendulum *pl*, the movements of which are transmitted to the tambour *k*, and by this recorded on a blackened surface. The instrument is first calibrated on a stream of known velocity.

The capillary velocity can be measured microscopically in thin tissues such as the frog's mesentery.

The Pulse

Blood enters the arterial system intermittently and leaves it at a constant rate. The arteries, therefore, at each beat of the heart accommodate their capacity to an increase in the volume of their contents. This they do through the elasticity of their walls. Every time the ventricle discharges its contents into the aorta part of the kinetic energy imparted to the blood is spent in distending the part of the aorta nearest the heart. The distended wall, in returning to its normal size, owing to its elasticity, exerts a pressure upon the blood—a pressure which is transmitted to the next segment of the aorta, which is distended in consequence. In this way is caused a wave of distension known as the pulse-wave, which travels peripherally at the rate of about seven metres per second. The transmission of the pulse-wave is therefore a purely mechanical effect, and is independent of any nervous agency, except in so far as the latter may influence the arterial tonus upon which the elasticity depends. The pulse-wave has nothing to do with the velocity of the blood, being much faster. As it travels towards the periphery the pulse-wave becomes less perceptible, the flow of blood from the arterioles into the capillaries being perfectly uniform.

The nature of the pulse-wave is investigated by means of the **sphygmograph**. This consists essentially of a spring which is pressed upon the radial artery at the wrist. The expansion of the artery is transmitted through the spring, magnified by a system of levers, and recorded on blackened paper which is moved by clockwork. Such a record is shown in Fig. 18. The wave will be seen to consist of a sharp upstroke and a slower downstroke. Upon the latter there is invariably a smaller elevation. This is known as the **dicrotic wave** (*e*), the notch preceding it (*d*) being called the **dicrotic notch**. The notch is due to the fall in pressure consequent upon the cessation of the outflow from the

ventricle. The dicrotic wave is due to a rebound from the closed aortic valve. It cannot be due to reflected waves from the periphery, since there is always the same interval between it and the main wave, whatever the distance from the heart. The dicrotic wave corresponds to the rise at 4 in the aortic-pressure tracing of Fig. 10. 11.

The sphygmographic record is subject to considerable variation even in normal individuals. Secondary waves may appear, due to reflected waves from the periphery, to vibration of the arterial wall, and to instrumental error. When there is a high blood-pressure owing to resistance to the outflow of blood from the arteries, the upstroke is more prolonged and may show upon it a secondary wave: such



FIG. 18.—Radial pulse. (From Starling's *Principles of Physiology*.)

a pulse is called **anacrotic**. When the outflow is freer the upstroke tends to be sharper, and a secondary wave appears in a pre-dicrotic position on the downstroke—a **catacrotic** pulse. Secondary waves which are post-dicrotic in position are of instrumental origin.

BLOOD-PRESSURE

Measurement

The arterial blood-pressure is measured directly in animals by the insertion of a cannula into the artery. This is connected with a mercury manometer. On the open surface of the mercury there is a float which holds a writing pointer. The cannula and tube between the blood and the mercury are filled with sodium sulphate, which prevents clotting.

Clinical Methods

For clinical purposes the **sphygmomanometer** is employed. The Riva-Rocci pattern, which is the one most commonly used, consists of a canvas band which is tied round the upper arm. On the inner side of the band is a rubber bag which, on being inflated with air, compresses the arm. The air inside the bag communicates with a pump, with a mercurial or spring manometer, and through a valve with the external air. Air is pumped in until the radial pulse can no longer be felt. The pressure is then gradually released by opening the valve, and the reading of the manometer noted at which the pulse just becomes perceptible. This gives the **systolic pressure**.

By an adaptation of this instrument it is possible to estimate the diastolic as well as the systolic pressure. When the pressure as recorded by the manometer is such that the pulse is barely perceptible, it means that the brachial artery is completely compressed except at systole, when the pressure within the artery is *just* sufficient to overcome the pressure tending to obliterate the artery. As the external pressure is gradually reduced the systolic pressure comes through more easily, *the artery being still compressed at diastole*. It is obvious that when the external pressure is just sufficient to compress the artery at diastole, the extra pressure produced in the artery by systole will exert its maximum dilating effect. If the oscillations of the manometer be recorded on a writing surface, as in Gibson's apparatus, the point at which the excursion of the lever is greatest marks the diastolic pressure.

The diastolic pressure can also be estimated by listening through a stethoscope placed over the brachial artery at the elbow. Beginning with complete obliteration of the pulse, as the pressure is released faint sounds are heard when the systolic wave begins to come through. With further lowering of the pressure a stage is reached at which the sounds suddenly become louder and sharper. From this

point they first become still more intense and then suddenly become faint. The reading of the manometer at which the sounds are loudest is the diastolic pressure.

The **mean pressure** is the mean between the systolic and the diastolic pressure. The **pulse-pressure** is the difference between the systolic and diastolic pressures. It is a measure of the output of the heart.

A rough indication of the arterial pressure can be obtained by placing two fingers upon the radial artery. The proximal finger exerts the pressure and the distal finger detects whether the pulse comes through or not. Certain characteristics of the pulse are recognised clinically. The

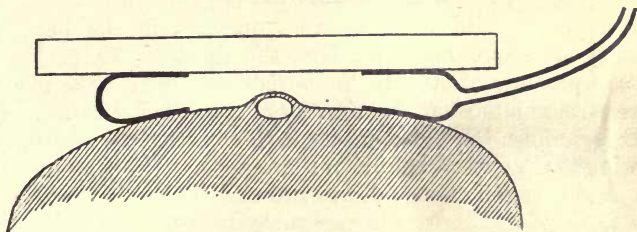


FIG. 19.—(From Starling's *Principles of Physiology*.)

volume is the difference between the diastolic and systolic pressure; it is therefore identical with pulse-pressure. The **tension** is the pressure during diastole.

The Measurement of Venous and Capillary Pressure

A rough estimate of the pressure in the subcutaneous veins of the upper limb can be obtained by raising the arm and noting the height above the heart level at which they become blanched. Another method is by means of the apparatus shown in Fig. 19. It consists of a rubber bag, on the opposite sides of which are two holes. The bag is placed on the skin so that one hole is opposite a vein. Over the other hole is placed a plate of glass. The junction between bag and skin and between bag and

plate are made air-tight by greasing. The bag is connected with a pump and manometer. At a certain pressure the blue colour of the vein disappears. A similar apparatus of smaller size is used for subcutaneous capillaries. This method does not give accurate results, since the resistance of the skin is unknown. The same objection applies to **von Kries's** method for measuring capillary pressure. In this method a glass plate of a certain area is pressed upon the skin and weighted until the skin is blanched. On dividing the weight by the area of the plate the pressure upon unit area of skin is obtained.

The Regulation of Blood-pressure

In young adults the systolic pressure in the brachial artery is about 110 mm. Hg., the diastolic 70, giving a mean pressure of 90. In the horizontal position the blood-pressure is almost uniform in large and small arteries. In the arterioles the blood meets with considerable resistance owing to the narrow calibre of the vessels. The consequence is that between the small arteries and the capillaries there is a considerable drop in pressure, from 90 in the former, to anything between 40 and 15 in the latter. The pressure in the veins is lower again than that in the capillaries. It varies between 10 and 0 mm. Hg., and in the great veins entering the heart may even have a negative sign. It will be seen that as the blood flows through the systemic circulation the pressure which it exerts upon the vessel walls does not fall uniformly. The greatest resistance to the flow of blood is met at the junction of the arterioles with the capillaries. In overcoming this resistance the blood falls from a region of high pressure in the arteries to a region of low pressure in the capillaries and veins. On this account we may regard the arterial system as a kind of reservoir. The purpose which such a reservoir serves will become clear when we consider under what conditions and by what mechanism the pressure of blood within it is liable to alteration. For the moment it will suffice to point out

that the maintenance of the normal blood-pressure is of the greatest importance, and that the body possesses an elaborate mechanism for maintaining a constant blood-pressure in the face of any tendency to disturb it.

It will be convenient here to consider in a general way the factors upon which arterial blood-pressure depends.

For a proper understanding of this question it is necessary not to lose sight of the fact *that the blood is circulating at a considerable rate—that we are dealing with a dynamic and not a static condition*. Blood-pressure is *caused* by the heart-beat, and is *supported* by the resistance in the arterioles.

Blood-pressure depends upon four primary factors—

1. The output of the heart.
2. The peripheral resistance.
3. The volume of the circulating blood.
4. The relative distribution of the blood, at any given moment, between the heart, arteries, capillaries and veins.

1. *The Output of the Heart*.—If the peripheral resistance is unaltered the arterial pressure will vary directly with the output of the heart. If the latter is increased the blood-pressure will rise.

2. *The Peripheral Resistance*.—This is the resultant of two factors—the viscosity of the blood and the calibre of the arterioles. Of these the latter is the more important. The output of the heart being constant, the blood-pressure varies directly with the resistance.

3. *The Volume of the Circulating Blood*.—The pressure will vary with the volume of the blood, provided that the distribution of the blood between the several parts of the circulation is undisturbed.

4. *The Distribution of the Blood*.—The capillaries and veins are, as we shall see, capable of considerable alteration in capacity at low pressures. A change in the capacity of the capillaries does not constitute a change in the peri-

pheral resistance, for the capillaries are beyond the site at which this resistance principally occurs—the arterioles. If two reservoirs at different levels are connected together with a narrow pipe, the resistance which the water meets in passing through the pipe is unaffected by the size of the lower reservoir. The variations in the capacity of the circulation other than the arterial part will affect the blood-pressure only by altering the proportion of the blood which is in the arteries at any given moment. We shall see that under certain circumstances a low blood-pressure may even be associated with constriction of the arterioles, when the capillaries are greatly distended. Under these conditions the blood is nearly all in the capillaries.

Such being the effect upon blood-pressure of changes in any one of the factors upon which it depends, the position becomes more complicated when more than one factor varies at a time. If the output of the heart and the peripheral resistance increase simultaneously, it is to be expected that the resulting rise in pressure will be greater than if either of these factors were to act alone. But if an increase in the cardiac output takes place concurrently with a decrease in the peripheral resistance, the two changes may so antagonise one another as to leave the blood-pressure unaltered. The *net* effect upon the circulation is *an increase in the velocity of the blood*.

The above effects can readily be imitated on an artificial schema of the circulation. But in the living body the effects may be very different owing to the close interrelation between the several factors. This interrelation is partly direct, partly indirect through the intervention of the central nervous system. If, for instance, the arterioles be constricted all over the body, the pressure in the arteries is raised, that in the capillaries and veins lowered. The raised arterial pressure causes, reflexly, slowing of the heart (*Marey's Law*). But this is not the only way in which the heart is affected. The lowering of the venous pressure, as we have seen, causes by a direct

effect upon the heart-muscle a decrease in the output per beat (p. 70) and, reflexly through the vagus, slowing of the heart. The peripheral resistance may therefore be said to influence the heart in two ways, backwards through the arteries and forwards through the veins.

THE PERIPHERAL RESISTANCE

As already stated, the peripheral resistance is the resultant of two factors, the viscosity of the blood and the calibre of the arterioles. The viscosity of the blood is due partly to the plasma, partly to the corpuscles. It decreases with rise of temperature and increases with the CO_2 content. In the present state of our knowledge it is impossible to assess what effect such variations will have upon the resistance under physiological conditions.

Concerning variations in the calibre of the blood-vessels, our knowledge is much more extensive. In thin tissues, like the frog's mesentery or the rabbit's ear, such variation can be directly observed. In organs such as the intestines, kidney or limbs, changes in the capacity of the blood-vessels are inferred from changes in the volume of the whole organ. The organ is inserted into a **plethysmograph**, which consists of a box opening equatorially. In the box are two holes. One is for the blood-vessels. This is made water-tight by packing with vaseline. The other hole is to convey oil with which the organ is surrounded to a tambour connected with recording apparatus. When the organ expands oil is driven out of the box and raises the recording lever. A special form of plethysmograph used for the kidney is called an **oncometer**, and for the heart a **cardiometer**.

Another method applicable to small tissues is to measure the venous outflow. This has the disadvantage of entailing a loss of blood.

The factors controlling the calibre of the blood-vessels are two—*nervous* and *chemical*.

THE NERVOUS CONTROL OF THE BLOOD-VESSELS

Vaso-Constrictor Nerves

In 1852 Claude Bernard showed that in the rabbit when the cervical sympathetic was cut, the arteries of the ear dilated, and when the peripheral end of the nerve was stimulated, the vessels contracted. He thus demonstrated not only that the sympathetic conveyed vaso-constrictor fibres, but that these exerted upon the vessels a constant tonic action, removed by section of the nerve. Vaso-constriction is now known to be a function of the whole sympathetic system, and the origin of the impulses has been traced to a centre—the “**vaso-motor**” centre, situated in the floor of the fourth ventricle. From this region impulses are constantly passing down the cord, which they leave by the sympathetic outflow in the thoracico-lumbar region. When the cord is transected at the seventh cervical segment or higher, a maximal fall of blood-pressure occurs, and any organ inserted in a plethysmograph undergoes an increase in volume, owing to withdrawal of this vaso-constrictor influence from all the blood-vessels in the body which are provided with sympathetic fibres. When the cord is transected at the third lumbar segment the blood-pressure is unaffected, showing that no vaso-constrictor fibres issue from the cord below this level. The blood-pressure is similarly unaffected when the brain-stem is cut above the fourth ventricle, proving that the controlling centre is below this level. But when the fourth ventricle is itself destroyed complete fall of blood-pressure results. A region in the fourth ventricle therefore presides over the condition of the arterioles, and determines the resistance which these vessels present to the outflow of blood from the arterial reservoir.

Details of the paths taken by vaso-constrictor fibres are fully given in the section on the Autonomic System. It is sufficient to state here that all these fibres emerge

from the cord between the first dorsal and third lumbar segments, that the fibres which supply the abdominal and pelvic viscera pass, without interruption, through the sympathetic chain and have cell-stations in the collateral ganglia—the semilunar, superior and inferior mesenteric ganglia, and that fibres which supply the blood-vessels of the skin have cell-stations in the sympathetic chain from which post-ganglionic fibres emerge and travel to the periphery bound up in the ordinary nerve-trunks.

There appears to be no vaso-motor control over the arteries of the brain or the coronary arteries of the heart. In the pulmonary vessels vaso-motor influence is indicated by the constriction which occurs on the administration of adrenalin.

When a vaso-constrictor nerve is stimulated it will produce a double effect—first, a diminution in the blood-supply to the part of the body to which it is distributed; secondly, if the distribution of the nerve is sufficiently extensive, stimulation will, by diminishing the outflow from the arteries, tend to raise the general blood-pressure.

Vaso-dilator Nerves

Claude Bernard showed that the *chorda tympani* nerve on stimulation caused dilatation of the blood-vessels to the submaxillary gland, and that this occurred independently of secretion. This was the first demonstration that there exist nerves which on stimulation cause an inhibition of the tonus of the vessels. Vaso-dilator fibres occur also in the *nervus erigens* supplying the penis. In both these cases the vaso-dilator effect is sufficiently striking to warrant our believing the existence of nerves having this special function.

When we turn to the blood-vessels in general we find ourselves on more debatable ground. Do the sympathetic nerves convey vaso-dilator as well as vaso-constrictor impulses? The only positive information we have on

this point is the isolated fact that stimulation of the cervical sympathetic in the dog causes vaso-dilatation of the gums and soft palate.

After the administration of the drug, **ergotoxine**, stimulation of the abdominal sympathetic causes vaso-dilatation. This may be interpreted in two ways. The drug may paralyse the vaso-constrictors, and so bring out the action of the vaso-dilators, previously masked by the greater power of their opponents. On the other hand, it may be argued that ergotoxine acts by converting an excitor into an inhibitor effect, in the same way as strychnine converts an inhibitor into an excitor effect.

Passing to the somatic system, we find more certain evidence of the existence of vaso-dilator nerves.

It is possible to demonstrate that in the nerves supplying the limbs, vaso-dilator as well as vaso-constrictor impulses are conveyed. In the first place, the two sets of fibres are susceptible to different modes of stimulation. When the peripheral end of the cut nerve is stimulated by the ordinary interrupted current, vaso-constriction occurs; when by slowly repeated induction shocks, vaso-dilatation is the result. Again, when the nerve is stimulated two or three days after section, vaso-dilatation invariably occurs, pointing to a difference in the rate of degeneration between the two sets.

How do the vaso-dilator fibres emerge from the cord? Are they part of the sympathetic or not? When the posterior root of a segmental nerve is cut and its peripheral end stimulated, vaso-dilatation occurs over the area of distribution of the nerve. This cannot be due to stimulation of the sympathetic, since sympathetic fibres join the nerve more distally. There is here, then, a contradiction of Bell's Law, according to which the posterior root was regarded as purely afferent. The question which we now have to decide is this: Does the posterior root contain two kinds of fibres, afferent conveying sensation and efferent conveying vaso-dilator impulses, or are there but

one set of fibres capable of conveying impulses in both directions ?

When the skin in any part is irritated, the underlying vessels are dilated, as is well known. This might be regarded as a simple reflex action were it not for the fact that the effect occurs even after section of the nerve-trunk. But when the peripheral part of the nerve has degenerated, the effect is abolished. Here, then, is a mechanism which clearly involves the nerve-trunk, but neither the posterior root ganglion nor the spinal cord. The effect can only be explained by assuming that each of the fibres in the posterior root divides into two branches, one supplying the skin, the other the vessels lying beneath. When the cutaneous nerve-ending is stimulated the disturbance is propagated not only centrally but throughout the whole fibre, and an inhibition of the tonus of the blood-vessel results. This is therefore termed an *axon-reflex*. (Fig. 20, p. 88).

It would seem therefore that the posterior root contains not two kinds of fibres but one kind, which usually convey impulses in both directions. The impulses passing towards the periphery are termed **antidromic**.

Is there a nervous centre which on stimulation produces vaso-dilatation ? Such a centre has been stated to exist in the fourth ventricle, distinct from the vaso-constrictor centre, but this observation is not confirmed.

We may now summarise the position with regard to the nervous control of the blood-vessels. Nearly all the arterioles of the body are under the control of nerves which have a constrictor effect upon them. These nerves belong to the sympathetic system. Some arterioles, particularly those of the somatic system, are in addition supplied with nerves which have an inhibitory effect. These nerves are identical with the sensory nerves (*see* Fig. 20). In such vessels the tonus of the muscular coat is determined by the relative strength of these two antagonistic impulses, and it so happens that vaso-constrictor influences are usually

far the stronger. When a vaso-constrictor nerve is cut, impulses which were previously passing down it are abolished, and the arterioles which it supplies are dilated. But when a vaso-dilator nerve is cut there is hardly any constriction. The vaso-dilators, then, under normal conditions exert but a feeble, if any, effect.

Does the wall of the arteriole possess an inherent tonus independent of any nervous influence? It would

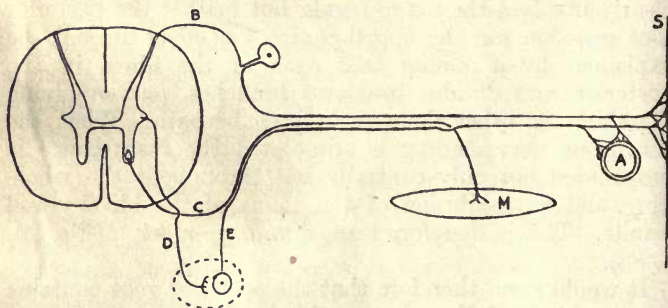


FIG. 20.

- B = Posterior Root Fibre, the axon dividing distally, one part supplying the skin, the other a blood-vessel *A* which it dilates.
 C = Motor Fibre to muscle *M*.
 D = Sympathetic pre-ganglionic fibre.
 E = Post-ganglionic fibre arising in a sympathetic ganglia. Distally it supplies the blood-vessel with vaso-constrictor fibres and innervates the hairs and sweat glands.

seem that it does, because when a nerve is cut the blood-vessels which it supplies, after first undergoing paralytic dilatation, acquire a certain degree of constriction.

Vaso-motor Reflexes

We now pass on to consider under what conditions these efferent mechanisms are brought into play. The vaso-motor centre or centres can influence, in two directions, the outflow of blood from the arteries. The tonus of the arterioles may be increased throughout the greater part

of the body. The blood is therefore held up in the arteries, and if the output of the heart is unaltered a rise in the arterial blood-pressure must result. This is called a **pressor** effect. On the other hand, a pre-existing normal degree of tonus may be reduced. Blood rushes out more quickly from the arteries, and the heart continuing unaltered, the blood-pressure must fall. This is known as a **depressor** effect.

It is to be expected that since the majority of arterioles receive a double nerve supply, constrictor and inhibitor, a pressor effect will involve both an excitation of the vaso-constrictors and an inhibition of the vaso-dilators, and similarly that a depressor effect will involve both an excitation of the dilators and inhibition of the vaso-constrictors. In other words, when the medulla is stimulated the changes in the calibre of the arterioles are produced by reciprocal innervation, in exactly the same way as movement at a joint. There is evidence that this is the case, but under normal conditions the vaso-constrictors are much more active than their antagonists, the latter appearing to play a minor rôle. Vaso-constriction may therefore be said to be produced principally by stimulation of the centre, vaso-dilatation by inhibition of the same centre.

The factors influencing the vaso-motor centre are of two kinds—nervous and chemical. Of the former it may be said that stimulation of any sensory nerve causes universal vaso-constriction. If a posterior root is stimulated an efferent antidromic impulse causes vaso-dilatation in the part supplied by the nerve, and an afferent impulse causes reflex vaso-constriction throughout the rest of the body, with consequent rise of arterial blood-pressure. In these two ways the part innervated by the nerve receives an increased blood-supply at the expense of the remainder of the body.

Among the nervous influences affecting the centre are the **psychical**. As is well known, vaso-constriction is one of the physiological expressions of emotional states.

But of all the factors which influence the vaso-motor centre, the one which in man is probably most often called into play is the **blood-supply to the brain**. It is evident that gravity must exert its influence upon the circulating blood. According to the position of the body, the pressure in the tibial artery varies from 165 mm. when the body is vertical, to about 105 mm. when it is horizontal. Yet the pressure in the brachial artery remains unaltered. It has already been mentioned that there is no evidence of the existence of vaso-motor fibres to the cerebral vessels. Alterations in the intracranial blood-pressure, due to gravity, are compensated by alteration in the facility with which blood can escape from the arteries in other parts of the body, chiefly the abdomen.

The **chemical influence** playing upon the centre consists in the reaction of the blood. In its extreme form this is seen if we asphyxiate an animal, having primarily cut the vagi to eliminate the effect of any action upon the heart. There occurs a rapid rise of pressure due, not to the specific action of carbonic acid, but to the increase in hydrogen ion concentration, for the effect can be imitated by injection of lactic acid into the blood-stream.

Depressor Reflexes

We have already seen that from the heart and beginning of the aorta arise afferent fibres which reflexly slow the heart. The same fibres reflexly produce fall of blood-pressure. This is not entirely due to slowing of the heart, since it occurs after section of the vagi. It is due to universal vaso-dilatation. Under what circumstances is this nerve normally brought into play? Of this we have no direct evidence, but it is assumed that the depressor nerve-endings are sensitive to conditions of excessive tension in the heart and aorta, and that when stimulated they reflexly ease the strain to which these organs are put. It is known that the rise in pressure during asphyxia is much less when the vagi are intact than when these

nerves are cut, but this difference can be explained as due to the direct stimulating effect of the carbonic acid upon the vagus centre.

THE CHEMICAL CONTROL OF THE BLOOD-VESSELS

(a) *Metabolites*.—It has long been known that blood percolates more freely through an organ as its content of CO_2 rises. Other acids—as, for example, lactic acid—have a like effect. This is due to a direct effect upon the arterioles and, as we shall see later on, the capillaries. When a tissue such as a muscle or gland becomes active, the acids produced dilate the neighbouring blood-vessels. But the same substances passing into the blood-stream stimulate the vaso-motor centre. These acids therefore produce two contrary effects—a *dilator effect, which is local*, and a *constrictor effect, which is general*. Locally, the dilator effect is greater than the constrictor. The result will therefore be an increased flow of blood through the active organ, and a decreased flow through the inactive tissues—in particular the viscera. More blood is diverted to the tissues which require it.

(b) *Pressor Substances*.—Adrenalin, the product of the suprarenal glands, has the same effect upon any organ as stimulation of the sympathetic nerve. It is itself discharged into the blood-stream when the sympathetic fibres to the suprarenal are stimulated. It follows, therefore, that when the sympathetic system enters upon a state of increased activity, as in emotional states or asphyxia, the physiological effect may be caused directly by nervous impulses passing to the various organs, or indirectly to the secretion of adrenalin. There is evidence that in the resulting rise of blood-pressure both factors contribute. It is sometimes found that in asphyxia rise of blood-pressure occurs in two stages: the first due to stimulation of the vaso-constrictor fibres, the second due to the action of adrenalin poured into the circulation.

But the rise of pressure which occurs on injection of adrenalin after the vagi have been cut is not entirely due to vaso-constriction. Adrenalin has also a direct action upon the heart, quickening it and increasing the amplitude of each beat. To the diminished output from the arteries is therefore added increased output from the heart.

THE CIRCULATION IN THE CAPILLARIES

We have seen that the arterioles, owing to their muscular walls, present to the flow of blood a resistance which can be varied by nervous and chemical means. The terminal arterioles lead into the capillaries—delicate tubes, about 0.5 mm. in length, composed of a single layer of flattened endothelial cells. These capillaries lie in a bed of lymph which separates them from the tissue-cells.

In the mesentery of the frog the circulation in the capillaries can be readily observed and compared with the circulation in the arterioles. In the latter it will be seen that the red corpuscles, owing to their greater specific gravity, run in the axis of the vessel where the stream is fastest. Surrounding the corpuscular column is a clear layer composed of plasma. Here the white corpuscles can be seen rolling in a leisurely manner along the inner wall of the tubes. When the capillaries are reached, owing to the narrowness of these vessels there is only one layer, the corpuscles passing one by one. Here the blood flows with great irregularity, stopping and rushing on alternately. There is no pulsation, this having been effectively damped by the terminal arterioles. Here, where the blood-flow is at its slowest, occur the transference of food material from the blood across the lymph to the cells, and of waste products from the cells to the blood, the exudation of lymph, and the migration of leucocytes into the tissue spaces. At present, however, we are concerned not with these nor with the dramatic changes which occur as the result of injury, but only with such modifications in the

capillaries as directly or indirectly affect the rest of the circulation.

Direct observation of the capillaries in the thin tissues of the frog has shown that they are capable of considerable variation in calibre. In a resting muscle *they are constantly contracting and expanding*, the great majority being at any one time contracted to complete obliteration of their lumen. The course of the blood is constantly changing; it flows now through this tube, now through that. The capillaries therefore possess a considerable power of contraction, and experiment shows that this power is independent of nervous influences, being *an inherent property of the endothelial cells of which the capillaries are composed*.

When a muscle becomes active there occurs a simultaneous opening up of all the capillaries, so that the blood supply may be increased several hundred times. The capillaries respond readily to chemical agents. On the direct application of acids they are dilated. It is therefore probable that the acids produced in activity are the cause of the dilatation.

It should be realised *that the degree of tonus of the capillaries is not dependent upon the blood-pressure*. The capillaries are not necessarily distended by a rise in the pressure of blood supplying them. Adrenalin, in addition to constricting the arterioles, in weak doses dilates the capillaries. Similarly, *histamine*, a base derived from the amino-acid histidine (by removal of CO_2), constricts arterioles and at the same time dilates capillaries.

Shock

Confirmatory evidence of the changes in calibre undergone by the capillaries is forthcoming from a study of the clinical condition of shock. This is characterised by a great fall of blood-pressure. It is brought on by trauma or hæmorrhage, especially under conditions of exposure to cold, excitement and deprivation of food.

The question arises, what has happened to the blood? It is not in the arteries, for these are constricted; it is not in the veins, for surgeons testify that these are not dilated. It must therefore be in the capillaries. In the paralysed and greatly distended capillaries a large proportion of the blood is accommodated. The blood corpuscles are to a great extent immobilised, like railway wagons on a siding. Secondary changes then occur owing to the deficient oxidation of the tissues. The stagnated blood, too, becomes concentrated in corpuscles owing to the excessive transudation of plasma into the tissue-spaces.

As regards *the cause of the capillary paralysis*, it has been found, as the result of observations on men wounded in the late War, that a relationship exists between the tendency to shock and the degree to which muscle is involved in the injury. Shock can indeed be produced experimentally by crushing muscles. It is therefore believed that substances resembling **histamine** in action are, in the destruction of tissue, liberated into the blood-stream. These paralyse the capillaries and lead to the stagnation of blood above described.

To what degree the capillaries, like the arterioles, are under nervous control is not determined. It is possible that the antidromic impulses which we have seen to constitute axon reflexes travel to the capillaries, and not merely to the arterioles.

THE CIRCULATION IN THE VEINS

In the veins the blood-pressure is 10 mm. Hg., and lower as the heart is approached. The blood is driven along the veins by two forces: the pressure of the blood behind it—that is to say, the kinetic energy communicated to it by the contraction of the left ventricle—and the negative pressure in front created by the contraction and relaxation of the right auricle. Two accessory factors combine in giving a further impetus to the venous flow. The first consists of

muscular contraction whereby blood is pumped through the capillaries into the venules. The second is the movement of the diaphragm—this muscle in descending tends to decrease the already negative pressure in the thorax and to increase the pressure in the abdomen. Most of the veins being provided with valves, muscular contraction in general, and contraction of the diaphragm in particular, are effective only in one direction—towards the heart. On account of the factors above described, the pressure in the great veins may be negative. Blood may be sucked rather than pushed into the heart. This is especially liable to occur during deep inspiration, for under these circumstances, to the negative pressure within the heart is added the negative pressure within the thorax, which tends to draw open the intrathoracic veins.

The nature of the jugular pulse has already been discussed.

THE PULMONARY CIRCULATION

The pulmonary circulation differs from the systemic in two important respects. First, the peripheral resistance is considerably smaller in the lungs than in the rest of the body. For this reason a smaller pressure is required to drive the blood through the capillaries. It is on this account that the right side of the heart is much less muscular than the left. In the second place, the capacity of the pulmonary circulation is continually undergoing rhythmic alteration, due to the alternate expansion and retraction of the lung tissue which occur in respiration. This influences the systemic circulation in two ways. First, each inspiratory movement of the chest aids the flow of blood along the extra-thoracic veins, in the manner above described. Secondly, in anæsthetised animals there is an effect upon the arterial pressure. During inspiration there is a quickening of the heart-beat due, as we have already noted, to diminution of vagus control. The effect upon

the blood-pressure is independent of the vagus and is purely mechanical in origin. There is a rise in blood-pressure during inspiration, and a fall during expiration. The blood-pressure and respiratory changes are, however, not synchronous—the blood-pressure is at its highest just after the end of inspiration, and at its lowest just after the end of expiration. With the distension of the pulmonary circulation more blood is presented to the left side of the heart, the output of the left ventricle is increased, and the blood-pressure in this way raised. The delay in the rise of pressure is due to the fact that at the beginning of inspiration blood first has to occupy the increased capacity of the pulmonary circulation before it affects the left side of the heart.

With the diminution in the capacity of the lung capillaries which occurs in expiration, there is first a further increase of the blood reaching the left auricle. Later, as the pulmonary vessels have constricted, the amount of blood fed to the left side of the heart is diminished and the blood-pressure falls.

These effects are reinforced by the movement of the diaphragm. As this muscle contracts it forces blood from the abdomen into the thorax, as already described.

In man the effects of the respiratory movement upon blood-pressure are exceedingly complex, varying with the form and depth of respiration.

Whether or no the pulmonary arterioles are subject to nervous control was for long a matter of controversy. By direct stimulation of nerves no positive evidence can be procured. Since, however, the vessels constrict to adrenalin, it is inferred that they receive constrictor fibres from the sympathetic.

CHAPTER VII

RESPIRATION

Introduction

RESPIRATION is the exchange of oxygen and carbonic acid between the organism and its surroundings. In evolution a special mechanism for the transport of these gases makes its appearance as soon as any of the tissues are excluded from direct contact with the medium in which the animal lives. A separate tissue, the blood, is developed principally, though not exclusively, for this function; the blood serving to carry oxygen from the external cells which can supply it to the internal cells which need it, and to drain the internal cells of the CO_2 which is constantly being formed within them.

With the appearance of land animals the process becomes complicated, owing to the fact that gaseous exchange now involves a change of state. Oxygen taken from the air has to be brought into solution, and CO_2 has to pass from solution into the free state. Moreover, the exchange of oxygen and carbonic acid between the animal and its environment occurs no longer on the surface of the body but in its interior—in the lungs. There are therefore no less than four stages in the process of assimilating oxygen. In the first, oxygen passes from the atmosphere to the air in the lung; in the second it passes into the blood; in the third it is transported in the blood to the whole body; in the fourth it passes from the blood to the tissues. Four corresponding stages occur in the removal of carbonic acid.

In considering how the cell acquires oxygen and rids itself of CO_2 we must bear this fact in mind—that *the extent of its gaseous interchange is determined not by the amount of oxygen presented to it by the blood, but by its own inherent need arising out of its metabolic activity*. It is the cell and not the blood which sets the pace for oxidation. The amount of oxygen which the cell utilises is therefore a measure of the work which the cell is performing. When the body as a whole is at rest the blood contains more than sufficient oxygen for its needs.

The problem of respiration resolves itself into two questions:—First, how are the supply of oxygen and the removal of CO_2 effected? Secondly, how do these vary according to the varying needs of the body? Consider the task which the blood performs. It conveys two gases in opposite directions, one of these gases being relatively insoluble in aqueous solution. This double transport of gases is carried out undisturbed by the many other functions which the blood performs.

THE TRANSPORT OF OXYGEN

Hæmoglobin

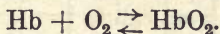
Hæmoglobin is a complex substance present in red blood corpuscles. It is a combination of hæmatin and a protein known as globin, and has a molecular weight of about 16,600. Its hæmatin component contains iron, each molecule of hæmoglobin containing one atom of this metal. Hæmoglobin possesses the property of forming with oxygen a loose compound known as oxyhæmoglobin. As each molecule of hæmoglobin combines with two atoms of oxygen, it follows that in oxyhæmoglobin there are two atoms of oxygen for every atom of iron. Hæmoglobin must therefore be regarded teleologically as a means of utilising the oxygen-combining property of iron, the great size of the hæmoglobin molecule overcoming the high specific gravity

of the metal. In other words, hæmoglobin is a kind of boat in which iron is enabled to float in the blood.

When oxyhæmoglobin is treated with potassium ferricyanide its oxygen is quantitatively evolved. The nature of the reaction is very complicated, for the oxyhæmoglobin is not reduced but is converted into a substance known as methæmoglobin, which contains just as much oxygen as oxyhæmoglobin. The oxygen, however, is in more permanent combination. Notwithstanding its complex nature, the process provides what is now the standard method for estimating the amount of oxygen originally present.

The combination of hæmoglobin with oxygen is a reversible reaction, the direction in which the reaction proceeds being determined by the pressure of oxygen to which the hæmoglobin is exposed.

The relation between the degree of combination and the oxygen pressure can be estimated by exposing a solution of pure hæmoglobin to different pressures of oxygen and estimating by the ferricyanide method the amount of the gas which has entered into combination. The result is expressed in the accompanying curve (Fig. 21 H), which is seen to be a rectangular hyperbola. It corresponds to the curve which is obtained theoretically from the equation



The respiratory function of hæmoglobin therefore lies in its capacity for combining with oxygen when the pressure of oxygen is high, as in the lungs, and of parting with the gas when the pressure is low, as in the tissues.

If, however, the dissociation curve of hæmoglobin in the blood resembled the curve for pure hæmoglobin, this substance would but inefficiently fulfil its function. Reference to Fig. 20 will show that even at as low an oxygen pressure as 10 mm. Hg the blood would still be 55 per cent. saturated; in other words, the affinity of hæmoglobin for oxygen would be too great for the transference of an adequate amount of blood to the tissues. In the body, however,

several factors contribute to modify considerably the combination of hæmoglobin with oxygen. These we shall now consider.

Factors Influencing the Dissociation of Oxyhæmoglobin

A. *Inorganic Salts*.—When the curves of dissociation of pure hæmoglobin and of blood are compared (Fig. 21), a

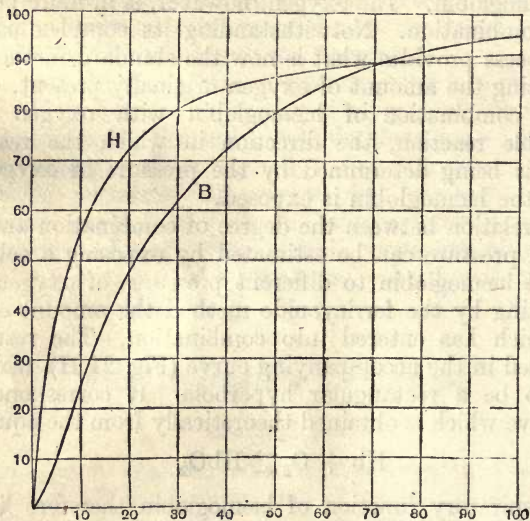


FIG. 21.—The dissociation curves of hæmoglobin (H) and of Blood (B). Ordinates; percentage saturation of hæmoglobin; abscissæ: pressure of oxygen in mm. (From Barcroft, *The Respiratory Functions of the Blood*.)

great difference is noted between them. While the former is rectangular the latter is more complex, the two differing in such a manner that at low oxygen tension dissociation takes place more easily from blood than from hæmoglobin, while at high oxygen tension more oxygen is in combination with the blood than with hæmoglobin. This means that the oxygen-carrying power of the blood from a place of

high to a place of low oxygen tension is superior to that of pure hæmoglobin.

This difference is due to the electrolytes, as is shown by the following facts—

1. If to hæmoglobin, salts are added, the dissociation curve approaches that of blood in the measure that the amount of salts present approaches that which obtains in blood.

2. The form of the dissociation curve of blood varies slightly, as does the saline content, in animals of different species. If to the hæmoglobin of an animal A are added salts as they occur in an animal B of another species, the curve obtained corresponds with the blood of B. Therefore the differences in the curves found in different species are due to differences not in the hæmoglobin, but in the saline constituents.

The salts are believed to exert their influence by causing a clumping together of the hæmoglobin molecules.

B. *The Reaction of the Blood.*—That the curve is materially affected by the degree of acidity of the blood is shown in Fig. 22, which gives the effect of varying amounts of CO_2 . Acidity increases the tendency to dissociation, the greatest effect being at an oxygen tension of 20 mm. At tensions of 80 mm. and over the difference is but slight. All acids have the same effect, the degree of their influence varying with the extent to which they form free hydrogen ions in blood.

C. *Temperature.*—The effect of temperature is shown in Fig. 22. With rise of temperature goes increased dissociation, an increase which is greatest at low oxygen tension.

We therefore see first that the combination of hæmoglobin with oxygen is of such a nature that it is readily influenced by three factors: the presence of salts, hydrogen ion concentration and temperature. We see, secondly, that these factors exert their greatest influence at low tensions of oxygen. We know, too, that of the three factors favouring

dissociation, two, namely rise of temperature and increased hydrogen ion concentration, and perhaps the third, alteration in the quantity of electrolytes, occur as the result of cellular activity. When the cell needs more oxygen, then the thermal and chemical effects of its activity are such as to increase the tendency of the blood to part with its oxygen to the tissues.

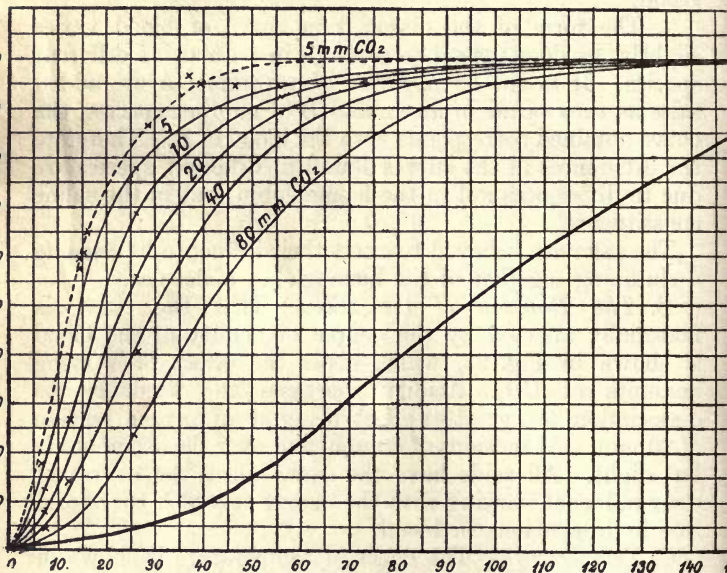


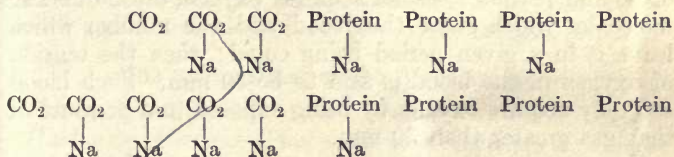
FIG. 22.—Dissociation curve of oxyhaemoglobin with different tensions of CO_2 . The lowest curve is at a CO_2 tension of 420 mm. Hg.

The Transport of CO_2

As this problem is intimately connected with the question of the reaction of the blood the reader is advised to refer to pp. 17–20. Here we may say that CO_2 is not carried in the blood as NaHCO_3 and dissociated in the lungs, for under the conditions in which it exists in the blood

NaHCO_3 is not dissociated. Nor is there conclusive evidence for the belief that CO_2 combines with hæmoglobin.

There are two mechanisms whereby the blood accommodates itself to varying amounts of CO_2 . The first is due to the *proteins of the plasma*. A protein, by virtue of the H atom of the COOH group, is an acid and is capable of combining with sodium according to the amount of sodium available, this in turn being determined by the amount of sodium required to combine with CO_2 . The sodium, in other words, shifts to and fro between the CO_2 and the proteins, the direction of the movement being determined by the amount of CO_2 present. Here is a diagrammatic representation—



Since the proteins are very weak acids, the amount of free protein does not affect the H. ion concentration.

The second method is the interaction between plasma and corpuscles already described (p. 19). When CO_2 is added to the blood, Cl ions pass from the plasma to the corpuscles, thus allowing sodium to enter into combination with the acid.

THE PASSAGE OF OXYGEN INTO THE BLOOD

From the alveoli of the lungs oxygen gains the blood by passing through the flattened cells of the lung epithelium, across the lymphatic space and through the endothelial wall of the capillaries. Is this process one of diffusion or is it due to active secretion of oxygen into the blood by the lung epithelium? If the process is to be explained by diffusion it is necessary to show that the tension of

oxygen in the blood leaving the lung is not higher than the partial pressure of oxygen in the alveoli. If, on the other hand, the pulmonary epithelium is capable of actively secreting oxygen into the blood, then the relation between the tension of oxygen in the blood and the partial pressure in the alveoli is of no importance.

Before proceeding further it is necessary that we should be quite clear as to what we mean by the tension of oxygen in the blood. The tension of a gas in a liquid is the pressure which it exerts in an atmosphere in equilibrium with that liquid, such pressure being independent of the pressure of any other gas present. Suppose that a sample of blood on exposure to air containing oxygen at a pressure of 30 mm. neither loses nor acquires oxygen, the number of molecules which enter the blood and the number which leave it in a given period being equal; then the tension of oxygen in the blood is said to be 30 mm. Such blood can only acquire oxygen by being exposed to a pressure of that gas greater than 30 mm.

Now suppose that there lies on the surface of the blood a membrane which has the power of absorbing oxygen from the air and passing it into the blood. Then the tension of oxygen in the blood will be higher than it would if no membrane intervened. The question before us is whether the lung behaves actively, like this membrane, or whether it is merely an inert partition freely permeable to oxygen. It is at once obvious that diffusion, if this occurs, must become more difficult as the pressure of oxygen in the alveoli becomes less. What happens at ten or fifteen thousand feet above sea-level where the pressure of oxygen is considerably diminished? Is the oxygen in these circumstances at a higher pressure in the alveoli than in the arterial blood? Further, supposing that the body is at the same time performing strenuous muscular work, will diffusion in a rarefied atmosphere allow of the passage into the blood of the increased amount of oxygen required? It is of course conceivable that both processes occur,

diffusion at high and secretion at low atmospheric pressure. There are therefore three possibilities; the process may be—

1. Entirely due to secretion;
2. Due to diffusion supplemented under special circumstances by secretion; or
3. Due to diffusion under all conditions.

That the lung should be capable of secreting oxygen is not an unreasonable supposition. Such a process is known to occur in the swim-bladder of the fish, which may contain as much as 80 per cent. of oxygen. At the same time, the swim-bladder is not a lung either in structure or in function.

In order to decide the nature of oxygen absorption two data are required, the partial pressure of oxygen in the alveoli and the tension of oxygen in the arterial blood.

The Composition of the Alveolar Air

This is determined by two methods.

Haldane's Method.—The apparatus consists of a tube one inch in diameter and several feet in length. At one end is fitted a mouthpiece, while two inches from it a short side-tube leads into a gas-receiver which is fitted at each end with a tap. At the beginning of the experiment the receiver is filled with mercury. The subject, after taking a normal inspiration, breathes into the tube as forcibly and as deeply as he can, and then stops the mouthpiece with his tongue. The end of the tube nearest to him now contains air which may be regarded as coming from the alveoli. On opening the taps this flows into the receiver, from which it can be analysed. The experiment is now repeated, but with this difference, that the forcible expiration into the tube takes place not after an inspiration, but after a normal expiration. The mean between the two samples is taken as the composition of the alveolar air. The normal oxygen pressure is found to be about 100 mm. of mercury.

Krogh and Lindhard's Method.—The subject breathes

normally through a tube provided with valves so arranged that the exhaled and inhaled air are kept separate. At the termination of *each* expiration the last fraction of air expired is collected in a side-tube. This method is said to give better results than Haldane's when strenuous exercise is being performed.

The Tension of Oxygen in the Blood

This can be determined in animals with a high degree of accuracy by means of *Krogh's Microtonometer*.

This is shown in Fig. 23.

The blood enters from the proximal end of the cut artery by the inner tube 1 (Fig. 23 A) and returns to the circulation by the tube 7. The stream issuing from 1 plays upon a small gas bubble 2 in such a manner as to agitate it violently. From time to time the bubble is drawn up into the graduated capillary tube by means of the screw tap 4 and its length measured. When this no longer changes, it shows that blood and bubble are in equilibrium. The bubble is now analysed in the apparatus by exposure in turn to caustic soda and pyrogallic acid.

The advantages of this apparatus lie in the relatively slight disturbance of the blood, in the small amount of air used—a bubble of only 2 mm. diameter—and in the relatively large surface exposed to the blood. Its disadvantages are that it is inapplicable to man, and that even in animals it cannot be used to determine the effect of exercise and other natural conditions. A further disadvantage is that in animals one cannot determine the composition of the alveolar air. Krogh had to be content with taking a sample of air from the bifurcation of the trachea.

Experiments conducted with this apparatus, so far as they go, show that the pressure of oxygen is always higher in the lungs than in the arterial blood—thus supporting the diffusion theory.

The Carbon Monoxide Method

Some years ago Haldane invented the following method for finding the tension of oxygen in human blood. The

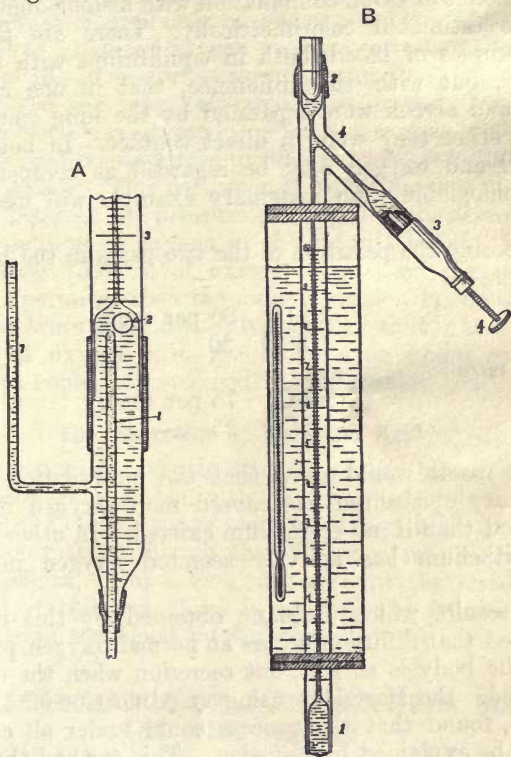


FIG. 23.—Krogh's microtonometer. A, lower part showing the gas bubble; B, upper part showing the fine tube into which the bubble is drawn for measurement.

subject breathes air containing a known amount of carbon monoxide. After a short time equilibrium is attained between the CO in the blood and the CO in the alveoli.

Some blood is then withdrawn and a sample of alveolar air taken. To this alveolar air is exposed *in vitro* blood taken from the subject before the experiment began. The amount of CO in combination with hæmoglobin in each case is estimated colorimetrically. There are therefore two samples of blood, both in equilibrium with CO and oxygen, but with this difference, that in one case the blood and alveoli were separated by the lung epithelium, in the other they were in direct contact. In both cases the CO and oxygen may be regarded as competing for the hæmoglobin. An imaginary example will make this clear.

Supposing the partition of the two gases in the blood *in vivo* were—

HbO ₂	80 per cent.
HbCO	20 „ „

and *in vitro*

HbO ₂	75 per cent.
HbCO	25 „ „

Such a result would show that the intervention of the pulmonary epithelium has caused more oxygen to enter the blood than if no epithelium existed. In other words, the epithelium has actively secreted oxygen into the blood.

The results which Haldane obtained by this method suggested that diffusion occurs at normal oxygen pressure when the body is at rest, but secretion when the oxygen is rarefied. But Hartridge, using a modification of the same method, found that the process could under all circumstances be explained by diffusion. This method therefore failed to decide the question.

Barcroft's Experiment

Recently a determination of the alveolar air and of the oxygen in the arterial blood at low oxygen pressures has been made by Barcroft in an experiment performed upon

himself. Barcroft lived for six days in a chamber in which the oxygen pressure was gradually reduced, the CO_2 exhaled being absorbed. On the sixth day samples of blood were taken from the radial artery during rest and after a period of work on a bicycle ergometer. The results show that at a reduced oxygen pressure corresponding to an altitude of 18,000 feet, while work is being done, the arterial blood is 83.4 per cent. saturated with oxygen, but when the same blood was exposed *in vitro* to a sample of alveolar air its oxygen content rose to 88.6 per cent.—a difference of 5.2 per cent. This corresponds to a difference of about 7.5 mm. between the pressure of oxygen in the alveolar air and the tension of oxygen in the arterial blood. During the exercise 750 c.c. of oxygen were used per minute. In this experiment then the oxygen tension in the arterial blood was lower than in the alveolar air—that is to say, the passage of oxygen into the blood even under extreme conditions could be explained by diffusion.

The Excretion of Carbonic Acid

The passage of carbonic acid out of the blood presents no problem comparable with the entry of oxygen. The pressure of CO_2 in venous blood is always higher than in the alveolar air, although the difference may sometimes be very slight. But taking into account the rapidity of diffusion of this gas, there is no difficulty in explaining its exit from the blood by diffusion.

THE INTERCHANGE OF GASES BETWEEN BLOOD AND THE TISSUES

Since there is no evidence of any storage of oxygen within the cell, we may assume that the passage of oxygen from the blood into the tissues is due to diffusion. In the case of carbonic acid there is a tension of this gas within the cell. We cannot estimate it directly, but we can arrive at some idea of it from the tension of CO_2 in the fluid

secretions, such as the lymph or urine. In these it may amount to as much as 70 mm. In the tissues it must be higher than this, since the greater part of the CO_2 is washed away by the blood and excreted in the lungs. We may safely say, therefore, that the passage of CO_2 out of the tissues, like the entry of oxygen, is due to diffusion.

We have seen that the dissociation of hæmoglobin is facilitated by rise in the hydrogen ion concentration and by rise in temperature. When the cell becomes active the increased tension of CO_2 and the rise in temperature which result affect the blood in such a manner as to make it more easily part with its oxygen. In other words, the chemical and thermal effects of increased consumption of oxygen cause an increased supply of oxygen.

LUNG VENTILATION

The ventilation of the lungs is effected by co-ordinated muscular movements which cause a rhythmic alteration in the capacity of the thoracic cavity. To this alteration the lungs adapt themselves owing to the elasticity of the lung tissue and to the potential vacuum of the pleural cavity.

The Muscular Mechanism

From a respiratory point of view the chest can be divided into two parts—an upper part, conical in shape, corresponding externally to the upper five ribs and internally to the upper lobe of the lung, and a lower part, almost cylindrical in shape, corresponding externally to the lower ribs and internally to the lower lobe. The changes in capacity which these two parts undergo differ both in kind and in the manner in which they are produced.

In the lower part of the chest the principal muscle involved is the diaphragm, which is aided in its action by the abdominal and the lower intercostal and interchondral muscles. The diaphragm is attached posteriorly to the spine by the crura and arcuate ligaments, and anteriorly

and laterally to the sternum and the lower ribs respectively. In its concavity lie the liver and stomach. In any downward movement of the diaphragm the abdominal viscera are depressed, and being incompressible must be accommodated by protrusion of the abdomen. The diaphragm and abdominal muscles are therefore antagonistic. If the abdominal wall is fixed, then the dome of the diaphragm cannot be depressed. Under such circumstances contraction of the diaphragm will have the effect of drawing the anterior and lateral attachment of the muscle up towards the dome. The attachment of the diaphragm to the lower costal cartilages draws the antero-lateral part of the lower ribs outwards and forwards, the subcostal angle being increased. Thus there is brought about an increase in the capacity of this part of the chest. Since the abdominal contents offer a certain resistance to the descent of the diaphragm, contraction of this muscle results not merely in a depression of its dome, but also in an elevation of its circumferential attachment. That is to say that in inspiration neither the dome nor the circumference is fixed, but the former moves downwards and the latter upwards.

Movement of the ribs is due mainly to the action of the intercostal and interchondral muscles, but owing to the variation in the size, shape and disposition of the different ribs no general rule can be laid down as to the manner in which these muscles act.

In the lower or cylindrical part of the chest the external intercostals, running as they do downwards and forwards, reduce the obliquity of the ribs and in this way assist inspiration. The internal intercostals, on the other hand, since they are directed downwards and backwards, cause expiration by increasing the obliquity of the ribs. This will be clear from the accompanying figures. *A* and *B* represent spine and sternum respectively, *C* and *D* two ribs. In the upper figure *xy* represents an external intercostal muscle. Imagine the four corners of the parallelo-

gram to be hinged. When xy contracts it must cause the ribs to move upwards in the direction shown, since such

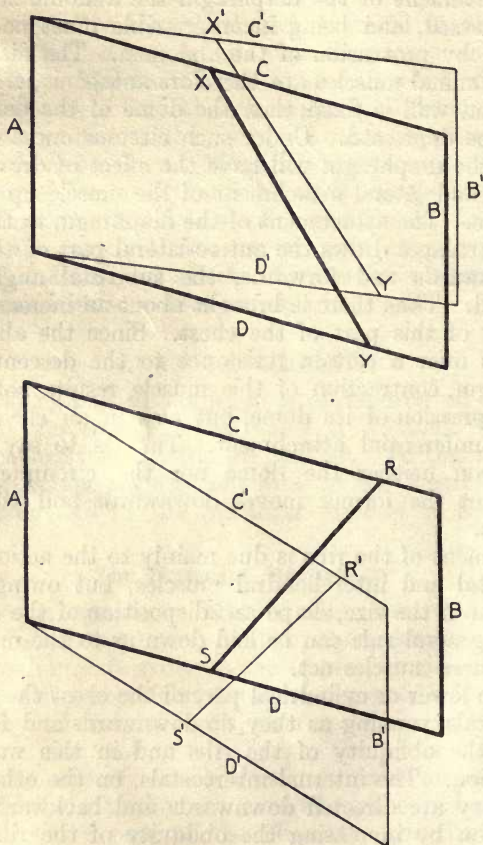


FIG. 24.—Action of the intercostal muscles.

movement will cause the ends of the muscle to approximate. The area of the parallelogram will be increased.

In the lower figure, *rs* represents an internal intercostal muscle. When this contracts the ribs are depressed, the area of the parallelogram becoming diminished.

But in the upper conical part of the chest the above considerations do not apply, for the costal movement consists during inspiration in a closing up of the upper six ribs towards the first, which is fixed. This is brought about by simultaneous contraction of the external and internal intercostals. As each rib is an arc of a wider circle than the one above it, this movement causes an increase in the capacity of this part of the chest.

The capacity of the chest is further increased in inspiration by extension of the spine.

Expiration is due not to a passive recoil, but to a co-ordinated muscular movement the reverse of that which causes inspiration.

Expansion of the Lung

The movement of the lung takes place *from the apex* downwards, forwards and outwards. In this movement the root of the lung participates. Indeed it is only owing to this movement of the root that any expansion can occur in that part of the lung which lies between the root and the posterior wall of the thorax.

During expansion and retraction the posterior part of the apex remains practically stationary. From the comparative disuse of this part of the lung arises its great liability to tuberculous infection.

The degree of expansion increases from the apex where it is slight, to the base where it is considerable.

In the upper conical part of the chest there is no relative movement between the chest wall and the lungs, but in the lower part the lungs glide up and down beneath the ribs.

The whole of the lung tissue does not expand equally. The root and the tissues in its neighbourhood expand least, whilst the greatest expansion occurs in the infundibula into which the alveoli open. The amount of air breathed

in and out at each respiratory excursion being smaller than the total capacity of the lungs, a complete interchange between the atmosphere and the lungs does not take place at each respiration. The result of this is that the temperature of the entering air is raised by that of the outgoing air, so that the former is almost at body temperature by the time it reaches the alveoli.

The walls of the bronchi are held open by the pull upon them of the elastic lung tissue, in antagonism to which are the constrictor muscles of the bronchi, which tend to keep the passages shut. The bronchial muscles are under the control of the vagus, which exerts a constant tonic influence over them. On stimulation of the peripheral end of the vagus these muscles are contracted.

During inspiration the passages are dilated by the increased pull of the lung tissue, and during expiration slightly constricted. In asthma the bronchial muscles undergo spasmodic contractions. The patient therefore makes violent inspiratory efforts to keep the tubes open.

The Exchange of Gases between the Lungs and the Atmosphere

The composition of inspired air, expired air and alveolar air is here shown, excluding water vapour, with which expired and alveolar air are saturated.

	Inspired Air.	Expired Air.	Alveolar Air.
Oxygen	20.96	16.4	15.0
Nitrogen and allied elements	79.00	79.5	79.0
CO ₂	0.04	4.1	6.0

The following are the volume changes induced—

The volume breathed in normal inspiration = 300–500 c.c. (*Tidal air*).

The volume which can be inhaled by an effort, super-

imposed upon a normal inspiration (*Complemental air*) = 1500–2000 c.c.

The volume which can be exhaled by an effort after a normal expiration (*Supplemental air*) = 1500–2000 c.c.

The total change of capacity, full inspiration and full expiration (*Vital capacity*) = 3300–4500 c.c.

Even after the greatest expiratory effort, the *residual air* remains, measuring 1500–2000 c.c.

THE REGULATION OF RESPIRATION

For the proper ventilation of the lungs two things are necessary, an orderly alternation of inspiration and expiration and an adaptation either of the extent or the rapidity of the movement to the needs of the body. We therefore have to consider how the rhythm is maintained and how it undergoes variation.

Respiration is dependent ultimately upon the integrity of a centre situated in the floor of the fourth ventricle near the nuclei of the vagus. When this centre is destroyed respiration immediately ceases. But respiration is a co-ordinated muscular act, and must therefore be due to the stimulation of motor centres in the cord—the centre for the phrenic nerve in the third, fourth and fifth cervical segments, those for the intercostal nerves in the thoracic region. The co-ordinated action of these centres is due to stimuli which they receive from the medulla, since the intercostal movements are abolished after section of the cord in the lower part of the cervical region, and both intercostal and diaphragmatic movements are paralysed after section through the upper part of the cervical region. Section of the brain-stem above the medulla is without effect upon the respiratory movements.

Respiration is under the control of the will only to a limited extent. We may cease breathing for a time or we may breathe excessively, but in either case the effort is short-lived and is followed by a compensatory effect,

hyperpnœa or apnœa, as the case may be. Voluntary effort, therefore, though it may affect the respiratory movements temporarily, does not affect the ultimate gaseous exchange. The increased respiratory movements which accompany a great need for oxygen, as in exercise, are brought about involuntarily.

In 1905 Haldane and Priestley showed conclusively that the activity of the respiratory centre is influenced by the composition of the blood supplying it. Their results may be thus summarised—

1. The partial pressure of CO_2 in the alveolar air is constant for each individual when in the resting state. It is about 40 mm.

2. The tension of CO_2 in the blood *leaving* the lung is equal to its pressure in the alveolar air.

3. Any change induced in the pressure of CO_2 in the alveoli is transmitted to the arterial blood.

4. When CO_2 is injected into the blood supplying the medulla respiration is increased.

5. A very slight rise of CO_2 alveolar pressure causes increased depth and rate of respiration.

The chain of evidence is therefore complete that the extent of pulmonary ventilation depends upon the tension of CO_2 in the *arterial* blood.

Carbonic acid, however, is not the only substance which affects the medulla. Any acid has a similar effect. The responsible factor is now known to be the hydrogen ion concentration of the blood.

The question now arises whether the tension of oxygen has also an effect upon the respiratory centre. Haldane and Priestley found that the tension of oxygen had to be very considerably diminished before any respiratory disturbance was produced. When increased respiration does occur under these circumstances, it is attributed not to deficiency of oxygen directly, but to accumulation of acids in the centres themselves owing to incomplete oxidation.

The comparative indifference of the respiratory centre

to the tension of oxygen leads to the phenomenon known as Cheyne-Stokes respiration, in which periods of breathing alternate with periods of respiratory rest. It occurs after the period of apnoea which follows excessive breathing. It is explained in this way. Owing to the excessive breathing which has just occurred CO_2 is to a great extent washed out of the body. The centre is then stimulated to activity by oxygen-want. By the respiratory movement thus caused the need for oxygen is immediately satisfied. The tension of CO_2 , being meanwhile still below normal, respiration ceases. This process is repeated until the tension of CO_2 regains its normal level and resumes the function of regulating the centre.

Cheyne-Stokes respiration is also found in certain toxic states. It is then attributed to the influence of the toxin upon the centre.

But the chemical constitution of the blood is not the only factor influencing lung ventilation. It is a matter of everyday knowledge that the orderly sequence of the respiratory movements may be interrupted by reflex stimulation. The stimulus may be emotional or it may be sensory, in the latter case originating from the surface of the body or from the respiratory passages. Since the most potent stimuli arise from the respiratory passages themselves, it would be natural to seek an effect upon respiration from the pulmonary nerve endings in the vagus.

What happens when the vagi are cut? On section of one vagus, respiration becomes slower and deeper; on section of both it becomes slower and deeper still, but the alternation of movements is undisturbed. But another change also occurs; for increased CO_2 tension now increases the depth of respiration still further, but the rate of respiration is unaltered. This would seem to show that one function of the vagus is to regulate the *rate* and to limit the *extent* of the respiratory excursion. What is the cause of the stimulation of the vagus? The answer to this is given by Head's experiment, in which it was shown

that artificial inflation of the lung (**Positive Ventilation**) caused cessation of breathing; standstill occurring in the expiratory position. Suction of air out of the lung, on

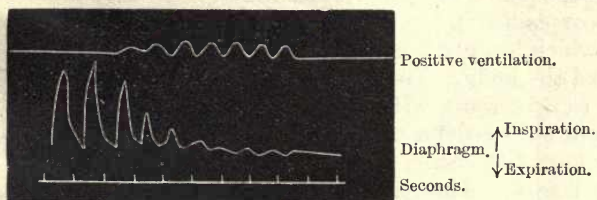


FIG. 25.—Positive ventilation.

the other hand (**Negative Ventilation**), is followed by cessation, but in the opposite phase; standstill now occurring in inspiration. These effects were found to be conditional upon the integrity of the vagi.

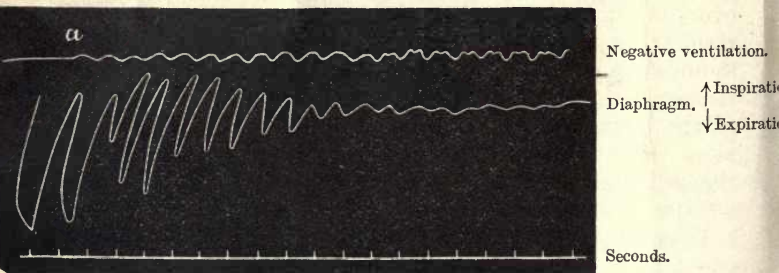


FIG. 26.—Negative ventilation.

The results show that on distension of the lung an impulse travels up the vagus which stimulates the medulla to produce relaxation of the diaphragm, while relaxation of the lung tissue, on the other hand, causes contraction of the diaphragm.

Head then proceeded to stimulate the vagus. Using the rabbit, where the nerve is free from depressor fibres,

he found that, on stimulating with a strong current, expiratory standstill was induced, but with a weak current inspiratory standstill occurred. He therefore concluded that the pulmonary branches of the vagus conveyed two sets of fibres, differing both in their sensitivity to stimuli and in their central effects.

Is the activity of the vagus thus experimentally produced a measure of what occurs normally? The only way in which this question can be answered is by testing the vagus for current of action. This is done by placing two non-polarisable electrodes on the trunk of the nerve and connecting them with the string galvanometer. The current of action waxes with inspiration and wanes with expiration.

We have already seen that respiration is practically unaffected by separation of the respiratory centre from the higher parts of the brain. But when this operation is combined with section of the vagi respiration ceases. Evidently the centre is affected by nervous impulses from two sources, normally from the vagus and vicariously from the higher centres.

We may therefore summarise the mechanism of the regulation of respiration as follows:—The respiratory centre is played upon by afferent impulses of two kinds, the chemical impulse of the hydrogen ion concentration of the blood and nervous impulses arising in the pulmonary nerve endings. Of these the latter have the effect of limiting the respiratory excursion, while the former is responsible for the adaptation of lung ventilation to the needs of the body. There is evidence, too, that impulses from the higher centres increase the susceptibility of the respiratory centre to the H. ion concentration of the blood. Whether the alternation of movement is due to rhythmic variation in the sensitiveness of one centre or to the alternating activity of two centres, one inspiratory the other expiratory, we do not know.

CHAPTER VIII

DIGESTION

Introduction

FOOD, in the form in which it is taken in by the mouth, is incapable of being of service to the body : first, because it is usually insoluble ; secondly, because even if soluble it is not in such a form as to be absorbed by the gut. To reduce the food into small molecules and to absorb these into the blood-stream are the functions of the digestive system.

In the process of digestion three physiological mechanisms may be said to be involved : the secretion of digestive juices, the action of enzymes upon the food, and the movements of the alimentary canal. As regards enzyme action we need only say here that this is invariably of the nature of hydrolysis, and that in the changes thus produced in the food-molecules there is no loss of potential energy. As regards the movements of the gut, these comprise an orderly sequence of co-ordinated movements. They serve to mix the food with the digestive juices, to propel the digesting mass along the canal, to expose it to the absorbing surface, and finally to evacuate such remnants as are not absorbed. As regards the secretion of digestive juices, some general remarks are necessary at this stage.

The Nature of Secretion

The formation of a secretion by a gland is associated with certain histological changes. When the fresh gland

is examined after a period of rest the cells are found to be filled with granules. After secretion these granules are much reduced in size and in number, those which are present occupying only the part of the cell nearest the lumen. The cell itself, instead of being distended as in the resting phase, has undergone shrinkage. Secretion, then, consists histologically of a breaking up of granules. Sometimes these are themselves discharged from the gland, but this is not usually the case, the secretion being generally quite clear. The granules are regarded by some authorities as constituting a store-house for the secretion, by others as constituting not only the store-house but also the seat of formation.

The act of secretion is accompanied by dilatation of blood-vessels. Vaso-dilatation, however, is not the cause of secretion, for at the onset of secretion there is usually a transient diminution in the volume of the gland. Moreover, vaso-dilatation may be unaccompanied by secretion, as when the latter process is abolished by drugs such as atropine. The dilatation of blood-vessels seems to be due to two factors: a direct effect of the stimulating agent, be it nerve or hormone, upon the blood-vessels, and an indirect effect due to the chemical products of secretory activity.

In some cases, as in the salivary glands, secretion is brought about by a reflex nervous action, in others, as in the pancreas, by a hormone or chemical substance elaborated elsewhere.

In the process of secretion there is, besides the formation in the gland of the specific constituent of the fluid secreted, a constant passage of water and other substances, from the blood to the cell and from the cell to the lumen. This cannot be due to filtration, for the secretion pressure in the duct may be greater than the blood-pressure within the gland. Attempts have been made to explain it by osmosis. It is held that the first change in the cell is a breakdown of molecules. This causes a rise in osmotic

pressure, which in turn causes water to pass into the cell from the blood. It is difficult to understand how continued secretion can thus be explained. Physical factors may play a part in secretion, but they cannot cause it. The best proof of this is that secretion is always accompanied by an increase in the consumption of oxygen and in the production of CO_2 . In the act of secretion, therefore, work is being done by the cells of the gland.

The salivary glands are innervated by branches from the cranial nerves and by the sympathetic. In the case of the submaxillary gland stimulation of the chorda tympani causes a secretion accompanied by vaso-dilatation, stimulation of the sympathetic, secretion accompanied by vaso-constriction. In some animals the chorda secretion is thin and copious, while the sympathetic secretion is thick and scanty. The question therefore arises whether this difference in the character and amount of the secretion is due to differences in the nerve fibres or to the accompanying differences in the state of the blood-vessels. It was believed by Heidenhain that each nerve contains two kinds of fibres, "trophic" fibres which cause secretion of water and salts, and "secretory" fibres which cause secretion of organic substances; in the chorda trophic fibres, and in the sympathetic secretory fibres preponderate. The following facts seem to support this view. The presence of meat in the mouth causes a secretion much richer in organic constituents than does the presence of acid. The difference is just as marked after removal of the superior cervical ganglia, indicating that different nerve-fibres in the chorda tympani are called into play.

Changes occurring in the Mouth

We habitually speak of the sight and smell and even of the idea of food making the mouth water. To what extent is this idea justified? For the full answer to this question we are indebted to the researches of the Russian physiologist, Pavlov. Pavlov diverted the duct of the dog's sub-

maxillary gland on to the outer surface of the cheek in such a manner that the secretion could be collected. He observed that, *provided the dog desired food*, sensations arising from the presentation to it of food evoked a secretion, even though the food did not come into contact with the mouth. Pavlov further showed that stimuli which normally were not connected with salivary activity could, by prolonged association, become effective. If, for instance, the exhibition of food was repeatedly accompanied by the ringing of a bell, after a time ringing the bell alone caused secretion. We can therefore readily understand how in human beings, in whom association of ideas is so much greater than it is in dogs, the range of stimuli may be very wide. Not merely the sight and smell of food, but the sounds and other sensations which we associate with the immediate prospect of gratification will effectively prepare the mouth for the reception of food.

The first cause of salivary secretion, then, is the combination of two stimuli: one, arising from within, the need for food; the other, arising from without, the sensation associated with the prospect of gratification.

But the food having entered the mouth, a fresh path for sensation becomes possible in the nerves of taste. These, too, as has been shown by Pavlov, cause reflex secretion of saliva.

In the salivary glands there exist two kinds of cells, differing in their histological appearances and in the secretion which they produce. There are the mucous cells, which secrete a viscid fluid containing mucin, and the serous cells, which secrete an albuminous fluid containing the enzyme ptyalin. The mixed secretion is alkaline in reaction.

The character of the saliva varies with the nature of the sensory stimulus from the mouth. Dry sand, for instance, provokes a profuse thin, meat a scanty thick secretion. It is said, too, that the amount of ptyalin increases with the amount of carbohydrate eaten.

The changes which the food undergoes in the mouth consist in a grinding up into fragments of about 2 mm. These, when impregnated and lubricated by the saliva, are ready for transference to the stomach.

The function of ptyalin is to convert starch into maltose, the action of the ferment occurring almost entirely in the stomach.

Deglutition

Deglutition is a complex process, or rather succession of processes initiated by a muscular movement under control of the will. The food is collected in a bolus on the dorsum of the tongue. It has to be transferred to the œsophagus, avoiding the nasopharynx and the larynx. Return to the front part of the mouth is prevented by the apposition of the upper surface of the tongue to the hard palate. A quick contraction of the mylohyoid and hyoglossus muscles draws the tongue upwards and backwards. At the same time the palatal muscles close the posterior nares by drawing the soft palate back to the posterior wall of the pharynx. The elevation of the hyoid bone, which occurs simultaneously, raises the larynx, the upper opening of which is closed by the descent of the epiglottis. By this co-ordinated movement the bolus is pushed down past the soft palate and posterior wall of the pharynx into the upper end of the œsophagus, which is stretched open to receive it. Coincidentally with this there is an inhibition of respiration. When the bolus enters the œsophagus it passes out of voluntary control, and normally out of consciousness.

The way in which food passes along the œsophagus depends upon its consistency. The ordinary bolus is carried down by a wave of contraction, which is initiated reflexly by the contact of the food with the pharyngeal wall. This wave becomes slower as it courses downwards. In the case of a thin fluid the propulsive force of the voluntary part of deglutition is sufficient to drive it with great

rapidity down to the lower end of the œsophagus, the completion of its journey into the stomach being performed more slowly. The fluid thus reaches the stomach before the wave of contraction which it has initiated while in the pharynx. This wave follows in the wake of the fluid, and serves to propel any remnants into the stomach.

The œsophageal contraction is dependent upon the discharge from the medulla of a succession of impulses which travel down the vagi. This is shown by the fact that the wave is interrupted by section of these nerves, but not by section of the œsophagus itself. But this wave of vagal origin is not the only form of contraction met with in the œsophagus. The tube is divided into two parts by differences in its muscular layer. There is an upper region, where the muscle is striated, and a lower region, where it is unstriated. When some days have elapsed after section of the vagi, the unstriated part develops the power of responding to pressure of food within it by undergoing peristaltic waves. These waves, which are quite independent of any voluntary act, eventually succeed in conveying the food from the lower end of the œsophagus into the stomach. The part played by these waves under normal conditions is described below.

The Cardiac Sphincter

Normally the cardiac sphincter is closed, but it opens on the approach of an œsophageal wave. When closed the tonicity of the muscle is not great, for it can easily be opened passively. It also opens on slight increase in the intragastric pressure. The part which the vagus plays in controlling the cardiac sphincter is complex, for on stimulation this nerve causes increased tonus followed by relaxation.

But although the sphincter is normally closed it opens rhythmically, and allows regurgitation of food into the lower part of the œsophagus. From here the food is returned to the stomach by a peristaltic wave originating in the unstriated part of the œsophagus. This wave is

independent of the act of swallowing and independent of the vagus.

Two conditions in the stomach notably increase the tonus of the cardiac orifice and inhibit its rhythmic relaxation—mechanical irritation and the presence of free acid in the cardiac sac.

THE STOMACH

The functions of the stomach are principally to act as a reservoir from which food can be discharged into the intestine at a regular speed, and to begin the breakdown of foodstuff and, in particular, of proteins. It possesses but a slight absorptive power.

Form of the Stomach

The stomach consists essentially of two portions, the cardiac and the pyloric, separated by the incisura angularis. The cardiac portion is further divided into two parts, the fundus or part above the level of the cardiac orifice, and the body or part below the fundus. Similarly, the pyloric part is subdivided into the pyloric vestibule—the main proximal part—and the pyloric canal, which consists of the distal 3 cm. and terminates at the pyloric sphincter.

The cardiac and the pyloric part of the stomach differ in their shape, in the structure of the glands which line them, in the character of the fluid which they secrete, and in the movements which they undergo.

All the gastric glands secrete pepsin, the principal gastric enzyme, but only those of the cardiac part secrete free hydrochloric acid, which is believed to be formed in the *oxyntic* cells.

The muscles of the stomach-wall are disposed in three layers—

1. An outermost longitudinal layer continuous with the corresponding layer in the œsophagus, but separated by a fibrous band from the longitudinal layer of the duodenum.

2. A middle circular layer forming a complete wall. It

is much thickened at the pylorus to form the pyloric sphincter, and slightly thickened at the cardiac end to form the cardiac sphincter, and opposite the *incisura angularis* to form the “*transverse band*.”

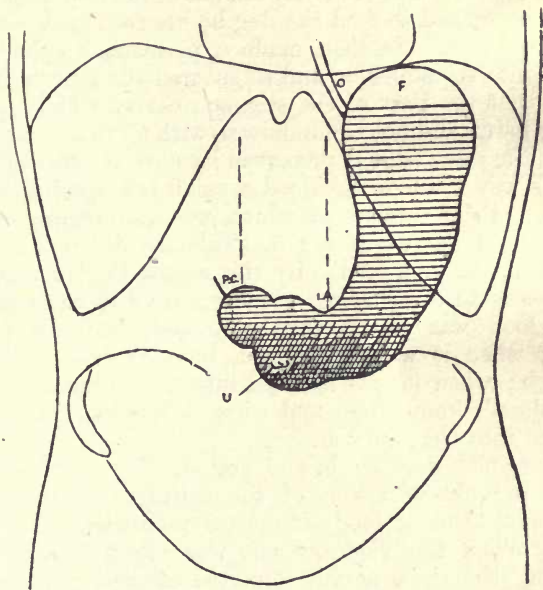


FIG. 27.—Position of human stomach after a bismuth meal (Hertz, from Starling's *Principles of Physiology*). O, œsophagus; F, fundus; I.A., incisura angularis.

3. An innermost oblique layer forming two bands passing from the cardia, one along the anterior, the other along the posterior surface. Near the pylorus they terminate in the circular layer.

The Secretion of Gastric Juice

As in the case of the salivary glands, our knowledge of

this process was put on a scientific basis by the experiments of Pavlov. Pavlov's procedure was as follows. He first cut the œsophagus in the neck, and brought the two ends to the surface, to which he sutured them. When he gave the dog food it merely fell out of the upper opening. When he wished to feed the dog he inserted food into the lower opening. He then made a permanent opening or fistula into the stomach, and so sutured the mucous membrane that the part of the stomach cavity which opened by the fistula did not communicate with the main stomach, but at the same time it preserved its normal nerve-supply. In this way there was formed a small sac opening to the exterior, the secretion of which was a measure of the secretion in the whole organ. This sac did not become contaminated with food. By this means Pavlov was able to investigate the changes which occurred in the stomach when food was shown to the animal, but not masticated; when it was masticated, but did not reach the stomach; when it was inserted into the stomach without the animal's knowledge; and when it was masticated and inserted into the stomach.

The results may be briefly stated. The same stimuli which provoke secretion of the salivary glands—sight, smell and taste of food—stimulate production of gastric juice. When the vagi are cut this effect is abolished, showing that these nerves form the efferent path of the reflex. Gastric secretion, therefore, begins before food has entered the stomach. It is important to notice that psychical secretion only occurs when the stimulus is associated with a pleasurable sensation. Mastication of inedible substances, like small stones, is ineffective.

The secretion of gastric juice continues long after the food has been taken. This is no mere prolongation of the reflex effect, for it occurs independently of the vagi when these nerves are cut after the preliminary secretion has begun. Nor is it due to the mechanical irritation of the food against the stomach-wall. It is due to the action of

the HCl and of the products of protein breakdown upon the pyloric mucosa. The substance thus formed is absorbed into the blood-stream, and, being conveyed back to the stomach by the arterial blood, stimulates the glands to continued activity.

In the process of gastric secretion there are therefore two factors. The first is a *nervous reflex* which starts the secretion; the second is the *stimulus of a chemical substance* or *hormone* which continues it. Thus the hormone which is the cause of the continuation of secretion is produced as the result of the initial secretion. This hormone has been called **gastrin** or **gastric secretin**.

The gastric juice produced by the chemical method differs from the juice of vagal origin in that it is adapted to the kind of food present in the stomach. It is most abundant with meat, while the presence of fats may altogether inhibit its formation.

Gastric Juice

Gastric juice has the following active constituents—

1. *Pepsin*.—This is formed in the gastric glands in an inactive form—pepsinogen, which is converted into pepsin on contact with hydrochloric acid. Pepsin requires free HCl, not only for its formation, but also for its digestive action; it is rapidly killed by alkalies. It causes an incomplete hydrolysis of protein, the end-products formed normally being proteoses and peptones.

2. *Rennin*.—This ferment, by converting the soluble caseinogen to insoluble casein, causes the coagulation of milk. Rennin is believed by some to be identical with pepsin.

3. *Gastric Lipase*.—Present in small quantities, it effects hydrolysis of finely divided fat.

4. *Hydrochloric Acid*.—This is secreted by the oxyntic cells of the fundus. Its functions will be described later.

Movements of the Stomach

As food enters it, the stomach expands in such a way that the *intragastric pressure is not raised*. That is to say, the stomach does not behave as though its walls were of elastic. The pressure upon its contents is the same whatever the degree of dilatation. How this remarkable effect is brought about is not known. The increase in circumference is more than can be accounted for by an elongation of the muscle fibres. It is therefore believed that these slide over one another in some way, the layers becoming fewer.

The stomach fills up from the pylorus to the cardia. A certain amount of air taken in at each deglutition is always present in the fundus.

The stomach is divided physiologically into two parts: the distal part, which undergoes peristaltic contraction, and the proximal part or cardiac sac, which has no rhythmic movement but which exerts a constant tonic contraction upon its contents. Owing to the quiescence of the cardiac sac and to the mucinous nature of the food, some considerable time elapses before the food is permeated by the gastric juice. During this period, which may last as long as an hour, the *hydrolysis of starch by ptyalin continues undisturbed*, being stopped only when the ferment is killed by the HCl.

Soon after the intake of food **peristaltic waves** appear at the transverse band, travelling towards the pylorus, about three waves occurring per minute. The seat of origin of the waves shifts gradually backwards till it reaches the middle of the body of the stomach. Each peristaltic wave kneads deeper into the stomach as it proceeds, and as it approaches the pylorus the longitudinal muscles contract with the circular. The sudden increase in pressure thus caused and the narrowness of the advancing ring causes the food to be driven partly through the pylorus if the sphincter allows, and partly backwards through the ring

of contraction. The effect of a succession of waves of this sort upon the gastric contents was shown by Cannon, who administered to an animal small capsules containing a large quantity of bismuth in a meal containing a small amount of bismuth. The capsules thus appeared by the X-rays as dark shadows in a faint shadow. At each wave the capsules were conveyed a short distance, until they slipped back through the advancing ring. They thus arrived by a to and fro movement at the pyloric vestibule. Finally, a wave carried them up to the pylorus, from which they were returned in the back-wash to the point from which they first started.

It is thus evident that gastric peristalsis has the effect of mixing very thoroughly the food and the gastric juice, and incidentally of exposing the mixture to the pyloric wall, thus favouring the formation of the gastric hormone already described. The cardiac sac meanwhile, by exerting a constant pressure upon its contents, keeps the gastric mill supplied.

As the stomach empties, diminution in its size affects first the middle of the body, which becomes tubular in shape. The part above this then diminishes until it is almost emptied. The pyloric part is the last to be evacuated.

The vigour of the gastric movement varies directly with the amount of HCl present, this acid, in fact, providing the stimulus to peristalsis.

As to the cause of the gastric movements, it is not certain how far they are *myogenic* and how far they are to be ascribed to *Auerbach's plexus*.

The Pyloric Sphincter

The pylorus remains firmly contracted during the whole of digestion except at regularly recurring intervals of momentary duration, during which it opens and allows a small part of the gastric contents to be squirted through. When this has happened it immediately closes again.

Many experiments prove beyond doubt that for the opening of the sphincter the presence of free acid on its gastric side is essential. It is equally proved that its closure is due to the presence of the same acid on its duodenal side—a local reflex mediated through Auerbach's plexus. But the action of the acid on the duodenal side is much the stronger, so much so that the presence of a very small amount of acid on this side is sufficient to counterbalance the antagonistic action of the large amount of acid in the stomach. The pylorus therefore opens only after the acid in the duodenum has been neutralised by the alkali secreted by intestine, pancreas and liver.

But the rate of emptying of the stomach varies with the nature of the food. It is slightly more rapid with carbohydrates than with proteins, and much more rapid with these than with fats. This difference has been shown by Cannon to be due to the effect of these foodstuffs upon the amount of free acid formed. Fats, as we have seen, inhibit the secretion of gastric juice. The slight difference between protein and carbohydrate is attributed to the combination of part of the HCl with the former, the effective acidity being thus reduced.

Absorption from the Stomach

The only substances known to be absorbed, and these only in small amounts, are peptones, sugars and alcohol. There is no absorption of water.

We may now summarise the **digestive changes** that occur in the stomach.

1. The digestion of starch continues in the fundus until the ptyalin is destroyed by HCl.
2. Proteins are hydrolysed incompletely to proteoses and peptones.
3. Milk is clotted.

4. Fats are liberated by the proteolytic digestion of their fibrous envelopes, and are to some extent hydrolysed by the gastric lipase.

5. Cane sugar is inverted to dextrose and lævulose.

6. In the early stage of digestion bacteria taken in with food decompose carbohydrates with formation of lactic acid.

7. These bacteria are destroyed by the HCl.

The **Hydrochloric acid** performs the following functions—

1. It activates pepsinogen and is necessary for the proteolytic action of pepsin.

2. It inverts cane sugar.

3. It destroys bacteria.

4. It maintains the closure of the cardiac sphincter.

5. It stimulates the stomach to peristaltic contraction.

6. It governs the opening and closing of the pylorus.

7. As we shall see later, it is necessary for the activation of the pancreas.

Vomiting

Vomiting is a reflex action induced by irritation of the stomach or of certain other parts of the body, particularly the alimentary canal. It may also be excited by irritation of the brain, as in tumours, or by emotions. It is usually preceded by a free flow of saliva, which is swallowed. Then come retching movements, which are really attempts at inspiration with the glottis closed. These culminate in the actual vomiting, which is a co-ordinated muscular act. The stomach is compressed by the simultaneous contraction of the diaphragm and the abdominal muscles. At the same time its walls undergo contraction. The gastric contents are thus driven out through the cardiac orifice, which is dilated.

When vomiting is violent, antiperistalsis of the small intestine may occur, driving the intestinal contents into the stomach.

THE SMALL INTESTINE

The small intestine is the seat of the greater part both of digestion and of absorption. The digestive changes are due to the action of juices derived from three sources, the pancreas, the liver and the intestine itself.

THE PANCREAS

The pancreas consists mainly of tubular alveoli, which are the seat of formation of the pancreatic juice. Separating the alveoli are the Islets of Langerhans, small masses of polyhedral cells not drained by any duct and having a more profuse blood supply than the alveoli. The Islets are believed to be concerned in carbohydrate metabolism, and to have no connection with the formation of the external secretion.

The Pancreatic Juice

This, the most active of all digestive juices, contains several ferments, of which the most important are the following—

Trypsin.—When the pancreatic secretion is collected from the duct without being allowed to come into contact with the intestinal epithelium, it has practically no action on proteins. But on addition of a small amount of intestinal juice it rapidly develops a strong proteolytic activity. From the fact that the degree of activity is independent of the amount of intestinal juice added, the action of the latter is concluded to be due to a ferment, to which the name **enterokinase** is given. The proteolytic ferment of the pancreas is therefore secreted in an inactive form—**trypsinogen**, the activated ferment being called **trypsin**. Trypsinogen on prolonged standing, even when kept sterile, becomes slowly active—the process being hastened by the addition of lime salts.

Trypsin, which acts only in alkaline solution, being, in fact, killed by acid, continues the gastric digestion of

proteins. While capable, like pepsin, of acting upon the native protein, trypsin differs from pepsin in that its action is more complete, for within an hour of tryptic digestion, amino-acids make their appearance. As the result of the action of this ferment, therefore, superadded to that of pepsin, proteins are converted into a mixture of peptones, polypeptides and amino-acids.

Accompanying the proteolytic action of trypsin, and probably due to the same ferment, there is a transient clotting of milk.

It appears that trypsin is destroyed in an alkaline fluid of the same degree of alkalinity as the contents of the intestine, but that this destruction is prevented by the products of its own activity. As these are removed by absorption the ferment is killed.

Amylase.—This enzyme resembles ptyalin in converting starch through the dextrin stage to maltose.

Lipase.—This ferment in the presence of alkalies converts fats into glycerine and soaps. It is indeed the principal lipolytic ferment in the body. Since its action is materially influenced by the bile, we shall discuss it more fully later on.

Maltase.—In neutral solutions pancreatic juice has some power of converting maltose into dextrose. The degree to which this occurs in the body will therefore depend upon the extent to which the juice is neutralised by the acid contents of the stomach.

The Secretion of Pancreatic Juice

Although the pancreas receives fibres, both from the vagus and the sympathetic, the amount of secretion which can be obtained by stimulation of either of these nerves is small and uncertain. Slight secretion begins within two minutes of the taking of food—evidently a nervous mechanism. But the onset of a full secretion coincides with the first appearance of food in the duodenum. It was shown in Pavlov's laboratory that the actual stimulus was the presence of HCl in that part of the gut, and that the effect

was produced even when the pancreatic nerves were cut. Bayliss and Starling showed that it occurred when not only the pancreas but also the duodenum was separated from the central nervous system. The mechanism, therefore, is entirely chemical. Neither acid alone nor extract of duodenal mucosa alone on injection into the blood is effective, but when the extract is first treated with HCl and the mixture injected a profuse secretion from the pancreas takes place. The substance thus formed, which differs from a ferment in being thermostable, Bayliss and Starling called **secretin**, and the substance in the duodenal mucosa from which it is produced they called **prosecretin**. Secretin is the best-known example of a hormone or chemical substance which, made in one organ, travels in the bloodstream to stimulate another organ to activity.

Since it is the acid of the gastric contents which causes the formation of secretin, it would appear improbable that the composition of the pancreatic juice changes in adaptation to the diet, except in so far as the nature of the food in the stomach alters the amount of acid secreted.

BILE

Bile, the secretion of the liver, is an alkaline, mucinous fluid of which the principal constituents are bile-salts, bile-pigments, cholesterol, lecithin and fats. It is continually being formed in the liver, from which it is secreted into the intestine either directly or after a period of storage in the gall-bladder. While in the gall-bladder it becomes modified by the abstraction from it of water, and the addition to it of mucin and nucleo-albumin. The significance of the gall-bladder appears to be related to the fact that bile is both a secretion and an excretion. As an excretion it has to be removed from the liver as soon as formed, owing to the toxic nature of the waste products which it contains; as a secretion it has to be passed into the intestine at intervals owing to its digestive action.

The bile-salts, which are sodium glycocholate and sodium

taurocholate, exert a profound influence over the digestion of fat by the pancreatic lipase. When the bile-duct is occluded nearly all the fat fails to be absorbed and appears in the fæces. Bile-salts possess the peculiar property of *lowering the surface tension between fat and water*. They therefore break up the fat into an emulsion, thus enormously increasing the surface upon which the lipase can work. Moreover, they dissolve the soaps which are formed by the lipase, and in so doing prevent the premature cessation of lipolysis which would otherwise occur owing to the formation of an insoluble coat of soap around each particle of fat. Further, there is reason to believe that bile has the direct effect of stimulating the pancreatic lipase.

The other constituents of the bile—bile-pigment, cholesterol and lecithin—are excretions, and play no part in digestion. The bile-pigments are bilirubin and biliverdin. They are partly excreted in the fæces as stercobilin, partly reabsorbed and excreted by the kidney as urobilin. Cholesterol and lecithin are products of metabolism of all tissues. In dissolving them the bile-salts perform yet another function.

The bile-salts are largely reabsorbed in the lower part of the small intestine and are returned to the liver.

The Antiseptic Action of Bile

Bile being a most perfect medium for growing intestinal bacteria, it is obviously the very reverse of an antiseptic, yet its absence from the intestine, as when the bile-ducts are obstructed, leads to increased bacterial activity. While it does not directly prevent the growth of bacteria, it reduces the quantity of protein pabulum on which they feed. This is due to its action in assisting in the saponification of fats, for the meat-fibres which are commonly enveloped in fat are thereby exposed to the action of the proteolytic enzymes. Further, bile by its presence increases the fluidity of the intestinal contents, and thus favours drainage.

The Secretion of Bile

The bile which pours upon the digestive mass is produced partly by contraction of the gall-bladder, partly by increased secretion from the liver. The unstriated muscle of the gall-bladder is innervated by the vagus and sympathetic. It is called into play by a nervous reflex originating in the duodenum. The exact path of the reflex is unknown.

Increased secretion of the liver has been shown by Bayliss and Starling to be effected by the same mechanism as secretion of the pancreas—that is, by secretin.

THE INTESTINAL JUICE

The succus entericus or intestinal juice is secreted from the whole length of the small intestine, but in amount diminishing from above downwards.

Alkaline in reaction, it contains the following ferments:—

1. *Erepsin*.—This ferment forms the third and last in the series of proteolytic enzymes. Without action upon proteins, it hydrolyses proteoses, peptones and polypeptides, converting them into amino-acids. By its means protein hydrolysis is completed.

2. *Enterokinase*.—This ferment has no digestive action of its own, but, as we have seen, activates trypsinogen.

3. *Maltase*.—Hydrolyses maltose to dextrose.

4. *Lactase*.—Present, at any rate, in the young; hydrolyses lactose to dextrose and galactose.

5. *Invertase*.—Hydrolyses cane sugar to dextrose and lævulose.

The Secretion of Intestinal Juice

Though some intestinal juice appears within a few minutes of the taking of food, a profuse flow does not occur until two hours after. The mechanism of secretion is not definitely known. Attempts have been made to assess the part played by the vagus and sympathetic in isolated loops of intestine, but the results are largely

vitated by the drastic operative procedure involved. It appears that secretin, as it influences the activity of the liver and the pancreas, influences also that of the upper part of the intestine. During the course of digestion there may be produced other hormones which cause secretion in the lower part of the gut.

A local secretion, produced through the agency of Meissner's plexus, occurs whenever a solid object touches the intestinal mucosa.

Movements of the Small Intestine

The digesting mass does not occupy the whole length of

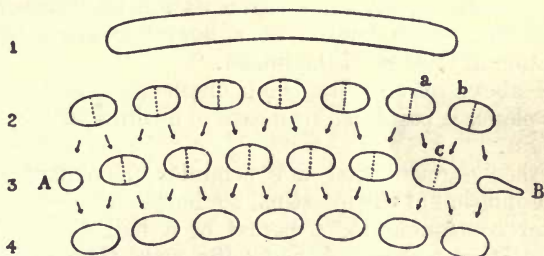


FIG. 28.—Segmentation movements (Cannon).

the intestine uniformly, but is grouped in segments of varying length, the intervening sections of the gut being practically empty. The food, after it has passed the pylorus, lies quiescent in the duodenum, where, of course, it receives the conjoint secretion of liver and pancreas. When by later additions from the stomach a certain length of gut is thus occupied, this part of the intestine undergoes **rhythmic segmentation**, the nature of which is best understood by reference to the diagram. As seen by X-ray examination after a bismuth meal, the continuous dark shadow suddenly breaks up into a number of segments separated by clear areas. After a few seconds, these segments as suddenly

divide, adjacent halves of neighbouring segments uniting together. The new segments again divide, with a return to the first. These changes occur in man at the rate of about seven per minute.

These movements favour both digestion and absorption; digestion by effecting a thorough mixture of the food with the digestive juices, absorption by affording the maximum exposure of the products of digestion to the intestinal mucosa. Moreover, the alternate constriction and dilatation of the intestinal blood-vessels facilitate the flow of blood, while at each constriction of the villi the material which has been absorbed is pumped into the portal vein and thoracic duct.

Accompanying rhythmic segmentation are the **pendular movements**, which consist in a lateral swaying without alteration in the size of the lumen.

The above movements, being unaffected when the local nerve plexus is paralysed by means of nicotine, are **myogenic** in origin.

Neither segmentation nor pendular movement causes any propulsion of the intestinal contents.

After continuing for a period of a half to two hours segmentation ceases. A **peristaltic wave** then moves the whole mass forward to a fresh section of gut where segmentation is renewed. A peristaltic wave consists of a wave of contraction preceded by a wave of relaxation. Its continuation after section of the vagi and splanchnics on the one hand, and its abolition after the application of nicotine on the other, prove it to be due to the local nerve centres—to *Auerbach's plexus*. When the gut is distended at any part there occurs contraction above and relaxation below the point of contact.

Two kinds of peristalsis are recognised—distinguished by their rapidity and by the length of intestine which they traverse. The more frequent is slow peristalsis, which travels at the rate of about 1 cm. per second, and after propelling the contents a short way, dies out. Its

purpose appears to be mainly to change the surface of absorption. Though propulsion of the food is involved, this is dependent principally upon the more rarely occurring **rush-peristalsis**, which, when fully developed, may sweep along the whole length of the intestine in about a minute. Peristalsis is more active in the upper than in the lower part of the intestine. At the approach of a wave to the lower end of the intestine the ileocæcal valve opens.

The vagus, while not causing the intestinal movements, nevertheless influences them in the direction of increased activity after initial inhibition. The sympathetic, on the other hand, inhibits all movement and tonus, and at the same time causes vaso-constriction, but it closes the ileocæcal valve.

Absorption from the Small Intestine

The small intestine is peculiarly adapted anatomically and physiologically for absorption; anatomically by its great length, by the folding of its internal surface into the valvulæ conniventes and by the projection from its mucous membrane of the innumerable villi; physiologically by the complex movements which it undergoes.

The food as it reaches the ileocæcal valve, though as fluid as it was when it entered the duodenum, is greatly diminished in volume and altered in composition, practically all the carbohydrates and the greater part of the fat and protein having been absorbed, together with most of the water.

The Nature of Absorption

How far are physical processes, such as osmosis, responsible for the passage of water and substances in solution? We may say at once that osmosis alone cannot account for the process, since not only water but saline solutions isotonic with blood and even the animal's own serum are

rapidly absorbed. Further, absorption of water is attended with increased oxygen consumption. Nevertheless, the process must be influenced in one direction or the other by the osmotic conditions. Hypertonic saline is usually absorbed only after a preliminary dilution, due doubtless to osmosis, while the absorption of hypotonic solutions is facilitated by the higher osmotic pressure in the epithelial cells. It may be mentioned, however, that absorption of hypertonic solutions may occur without preliminary dilution.

As to the form in which the three classes of foods are absorbed, this question is best deferred, since it has an important bearing upon the metabolic history of these substances. Suffice it to say at present that carbohydrates are absorbed only after hydrolysis to monosaccharides, proteins chiefly, if not entirely, after they have been broken up into amino-acids, and fats only after saponification into glycerine and soaps. After absorption, carbohydrates and proteins enter the blood direct, fats chiefly indirectly by the lacteals and thoracic duct.

THE LARGE INTESTINE

In different animals the large intestine varies in size relatively to the whole of the gut, according to the nature of the food which is habitually taken. Its large size in certain herbivora is associated with the extensive bacterial decomposition which takes place within it, and by means of which the cellulose of the food is converted into a form which is readily absorbed. But in man and carnivora this process does not occur, cellulose not being absorbed.

The digesting mass, as it passes through the ileocæcal valve, is as fluid as it was when it entered the small intestine. It enters the large intestine to a great extent deprived of nutriment. It consists of waste products, undissolved substances, bacteria and the digestive juices. In the large intestine this fluid mass becomes concentrated by

absorption of water, and the fæcal residue stored until ready for evacuation. The large intestine may be divided physiologically into two parts: a *proximal part*, consisting of the ascending colon and the neighbouring half of the transverse colon, whose function it is to provide a maximum exposure of the contents to the intestinal wall, and a *distal part*, consisting of the remainder of the colon, which is concerned in the storage of fæces and in the process of defæcation. From the nutritional point of view the principal function of the large intestine is the absorption of water. The glands of the intestinal wall give out a mucous secretion, which has no enzymes. It serves to lubricate the fæces. The chemical changes which occur are due to bacteria, with which this part of the gut swarms. Of these organisms the commonest is the *Bacillus Coli*.

The organisms feed principally upon proteins, and in particular upon certain products of protein hydrolysis—tyrosin and tryptophane. From tyrosin they form carbolic acid, from tryptophane scatol and indol, the substances responsible for the characteristic odour of fæces. The extent to which these compounds are formed depends first upon the amount of proteolytic products reaching the large intestine—that is to say, upon the efficiency of the digestive processes; secondly, upon the degree of stasis of the intestinal contents in this part of the gut. Phenol, indol and scatol are liable to be absorbed, and when absorbed are toxic. Normally, however, they are rendered less toxic by combination with sulphuric acid and excretion in the urine.

Besides these substances, there are formed certain nitrogenous bases usually known as “**ptomaines**.” Of these the commonest are histamine, cadaverine and putrescine. They are formed by removal of CO_2 from certain amino-acids—the work, again, of bacteria. If absorbed into the blood-stream they exert toxic effects.

Intestinal bacteria also act upon carbohydrates, converting them into lactic acid.

Movements of the Large Intestine.

Food begins to enter the large intestine *within three hours* of ingestion. As a peristaltic wave approaches the ileocæcal valve the colon in the neighbourhood of the valve first contracts, then relaxes as the wave discharges the food into it. The ileocæcal valve is a true sphincter, having a nervous mechanism of its own. It appears both from X-ray observations and from the direct observation of the intestine exposed in warm saline solution that the principal movement in animals consists of **antiperistaltic waves**. These begin at about the middle of the transverse colon, and at the rate of about five per minute (in the cat), sweep towards the cæcum. Prevented by the closing of the ileocæcal valve from regurgitating into the ileum, the contents escape distally through the peristaltic ring. By this means is ensured the maximum exposure to the absorbing surface. From the fact that enemata introduced at the rectum appear in cæcal fistulæ, the same process is believed to occur in man, though it has not actually been observed. The contents fill up the ascending colon, and as they proceed gradually attain the fæcal consistency. In the transverse colon the advancing column is split up by waves of contraction, which travel slowly towards the pelvis.

Normally the contents take about *two hours* to traverse the ascending colon, and another *two hours* to reach the splenic flexure. The part of the large intestine which lies between the middle of the transverse colon and the rectum is in a state of constant tonic contraction, interrupted only by slow peristaltic waves. These have the effect of filling this part of the intestine from below upwards. As they pass along, the fæces become gradually harder by absorption of water.

Defæcation

Defæcation consists of a train of events partly involuntary and partly voluntary. The fæces accumulate from the

lower end of the pelvic colon upwards to the splenic flexure, the rectum meanwhile being empty. The process of defæcation is initiated by a peristaltic wave, which pushes the distal end of the fæcal mass into the rectum. In different individuals various stimuli bring this about—the taking of food or a cold bath. It is a reflex which is developed by habit. The rectum is specially sensitive to distension—this being interpreted subjectively as a desire to defæcate. The rectal distension causes reflexly a strong wave of contraction, which travels downwards from the splenic flexure. This is accompanied by the inhibition of the internal sphincter ani. The efferent path for both these actions is by the sacral autonomic. This reflex action is reinforced by the voluntary act of contracting the diaphragm, the thoracic and abdominal muscles with the glottis closed.

If the call to defæcation—that is to say, the sensation aroused by distension of the rectum—is not obeyed, the sensation passes away, the result being that the rectum becomes filled with an accumulation of fæces to which it is insensitive. The reflex mechanism is thus thrown out of gear. After normal defæcation the bowel should be empty from the splenic flexure downward.

CHAPTER IX

GENERAL METABOLISM

Introduction

LIFE consists physiologically of a transformation of energy. Animals are dependent for their supply of energy upon the potential energy present in the food, this being derived in the first instance from the sun through the anabolic processes characteristic of plant-life. The energy thus presented to the animal is converted by it into a form which consists physiologically of cell-activity, and mechanically of work and heat. The extent of this transformation and its relation to the degree of activity are capable of estimation. The body, in other words, may be considered as a machine in which the energy supplied is balanced by the energy liberated.

But the body itself is not unaffected by the processes of combustion which take place within it. Cell-life involves a constant wear and tear which has to be made good. This process of disintegration and reconstruction, unlike the transformation of energy, cannot be measured, nor is its relation to cell-activity known.

The food when it enters the body undergoes one of two fates. In the first place it may serve merely as a supply of energy; its destiny is oxidation, and any changes which it may undergo other than oxidation are either for the purpose of storage or of the nature of preparation for combustion. In the second place the food may become a part of the cell itself, an essential cog in the wheel, its presence being necessary for the performance and for the

regulation of the chemical changes occurring in the cell. It controls the dynamic changes, but the energy which it itself possesses is not thereby utilised. Any changes which it undergoes consist in an adaptation to the part which it has to play. Now certain of the substances which form essential parts of the cell-structure cannot be synthesised in the body. Some are minerals, others can only be manufactured by plants. It follows that a quantitative consideration of the food, as a source of energy, is only valid when the adequacy of the food for the maintenance of the machine is guaranteed. To take an example. Supposing we wish to determine whether fat is necessary as a source of energy: were this merely an energy question it could easily be settled by feeding an animal on a fat-free diet. But it is known that on such a diet the animal will fail to live, not because the energy-supply is inadequate, but because of the loss of certain substances present in fat, which are constantly required by the body for effecting chemical changes within it.

The chemical changes occurring from the time of absorption to the time of excretion, and the transformation of energy involved therein constitute what is known as metabolism.

THE EXPENDITURE OF ENERGY

In this chapter we shall consider the body as a machine, and proceed to investigate quantitatively the transformation of energy involved in the processes of life. For estimating the amount of energy liberated two methods are employed—*Direct and Indirect Calorimetry*.

Direct Calorimetry

In this method the subject is put into a specially constructed calorimeter and the amount of energy estimated as heat is recorded. The most modern apparatus for experimenting upon man is that invented by **Benedict**. It consists of a chamber of the size of a small room in which the subject can live for a prolonged period. The

walls, ceiling and floor of the chamber are composed essentially of four layers separated by air-spaces. The outer two are of wood, the inner two of copper. The copper walls are connected together in an electric circuit in which is placed a thermo-electric junction and galvanometer. These register any difference of temperature between the two walls. The temperature of the outer copper wall can be varied by means of an electric heating apparatus. When any difference of temperature occurs between the walls it is annulled by heating or cooling the outer. There is therefore practically no loss of heat by radiation from the chamber. All the heat evolved by the subject is absorbed by a circulation of cold water through the chamber, and its amount calculated from the volume and rise in temperature of the water. But this does not include all the heat produced, for a certain amount is dissipated in converting water into water-vapour in the lungs. This is calculated by absorbing the water-vapour in the outgoing air with sulphuric acid and estimating the latent heat of its formation.

The unit of energy employed is the amount of heat required to raise one kilogramme of water through 1° C. This is called *the large Calorie (C.)*.

The accuracy of the apparatus, tested by burning a known amount of some inflammable substance in it, is found to be of a very high order.

When the individual is at complete rest almost all the energy is given off as heat. If it is desired to investigate the effect of muscular activity, a measured amount of work is performed on a pedalling machine. The work recorded is reduced to its heat equivalent, 1 Calorie being equivalent to 425 kilogramme-metres of work.

It is first necessary to determine whether the foodstuffs liberate the same amount of energy when metabolised in the body and when oxidised *in vitro*. It is obvious at the outset that accurate correspondence is not to be expected unless the oxidation which occurs within the body is as

The energy available by complete oxidation of a substance is determined by means of the **Bomb Calorimeter**, which consists of a steel case containing a known amount of the substance in an atmosphere of oxygen. This is immersed in a known volume of water. Combustion is effected electrically, and when completed the amount of heat evolved is measured. With this apparatus the following values have been determined—

1 gm. carbohydrate on combustion gives off	4·1 C.
1 gm. fat " " "	9·3 C.
1 gm. protein " " "	5·0 C.

Heat given out by the subject	.	.	4833 C.
Work done, calculated as heat	.	.	602 C.

Total energy liberated, calculated as heat 5435 C.

Indirect Calorimetry

Since the energy liberated on oxidation within the body is practically identical with that liberated on oxidation outside the body, it follows that if we know the amount

of each kind of food which is being metabolised we can calculate the energy liberated without recourse to a calorimeter. This can be done even without a previous analysis of the food administered, the only data required being :

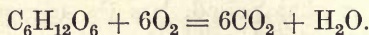
(1) *The total respiratory exchange*, (2) *the amount of nitrogen excreted*.

The Respiratory Exchange : Respiratory Quotient

The various methods which have been adopted for estimating the oxygen intake and CO_2 output fall into two groups : (a) The animal is placed inside a chamber through which air deprived of CO_2 and water-vapour is pumped. The total volume of air passing through is measured, and the oxygen and CO_2 passing out of the chamber estimated. (b) This method, more suitable for experiments upon man, consists in making the individual breathe through a suitable mask into a chamber which is supplied with a constant stream of oxygen, the oxygen admitted and the CO_2 expired and absorbed being estimated.

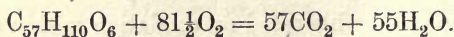
The relation between the amounts of CO_2 expired and of oxygen absorbed during the same period, expressed as the former divided by the latter ($\frac{\text{CO}_2}{\text{O}_2}$), is termed the **Respiratory Quotient (R.Q.)**. Its value varies according to the amount of oxygen already present in the food molecule undergoing combustion. This will be seen from the following equations—

Carbohydrate :



$$\frac{\text{CO}_2}{\text{O}_2} = \frac{6}{6} = 1.$$

Fat :



$$\frac{\text{CO}_2}{\text{O}_2} = \frac{57}{81\frac{1}{2}} = 0.7.$$

In the case of proteins, owing to their varying composition, the R.Q. is not constant. The average figure is 0.8. The proportion of nitrogen in protein is sufficiently constant to allow of the nitrogen excreted being a measure of the protein catabolised, one gm. of nitrogen corresponding to 6.2 gms. of protein which yields on oxidation 5.9 litres of oxygen, and 4.8 litres of CO_2 .

Knowing then the total respiratory exchange, and deducting from this the exchange which is due to the catabolism of protein as estimated from the urine, we are left with the respiratory exchange which represents the combustion of non-protein material. It only remains to determine how much is due to carbohydrates and how much to fats. This can be estimated from the R.Q. obtained from the non-protein respiratory exchange. If the figure obtained is 1.0, carbohydrates only are being metabolised; if 0.7, fats only, any intervening figure representing a certain proportion of carbohydrates and fats.

The following example (from Krogh) will make this clear.

Total gaseous exchange	= 405	litres O_2 and 331 litres CO_2 .
N. excreted, 34.93 gms. corresponding to	<u>206.9</u>	“ “ “ <u>166</u> “ “
Non-protein gaseous exchange	198.1	“ “ “ 165 “ “
Non-protein R.Q.	$= \frac{165}{198.1}$	$= 0.833$.

The figure 0.833 corresponds to a combustion of—

and $\left. \begin{array}{l} 0.51 \text{ gms. carbohydrate} \\ 0.293 \text{ „ fat} \end{array} \right\} \text{ per litre of oxygen.}$

The subject is therefore catabolising—

Protein . . .	34.93	\times	6.2	= 218 gms.
Carbohydrate. .	0.51	\times	198.1	= 101 „
Fat . . .	0.293	\times	198.1	= 58 „

Now, as stated above, 1 gm. protein on combustion gives off 5.0 C., 1 gm. carbohydrate 4.1 C., and 1 gm. fat 9.3 C.

The total heat-production in this case is therefore—

$$(218 \times 5.0) + [(101 \times 4.1) + (58 \times 9.3)] \\ = 2043.5 \text{ Calories.}$$

Here, then, is an indirect means of arriving at the energy production. Though simpler to work than the direct method, it is not free from certain fallacies. The first of these is that the actual production of CO_2 may not correspond to the elimination, owing to the capacity of the tissues for storing this gas. A second fallacy is that processes other than direct utilisation of the food-stuffs may conceivably be taking place. Supposing, for instance, that the body is storing fats after forming them from carbohydrates. In the conversion of an oxygen-rich into an oxygen-poor compound a certain amount of oxygen is liberated, and is presumably available for oxidation of other molecules. The consequence is that the amount of atmospheric oxygen needed by the tissues is diminished to a corresponding extent. In other words there will be an elevation of the R.Q. The abnormally high respiratory quotients (1.2 or 1.3) observed in hibernating animals at the onset of the dormant period, and in geese when they are fed with large quantities of carbohydrates, have been taken to prove the conversion of carbohydrate into fat.

A third fallacy lies in the fact that CO_2 may be produced by processes other than oxidation in the tissues. In herbivorous animals a large amount of CO_2 is formed in the intestine by bacterial decomposition.

Intestinal fermentation, then, and conversion of carbohydrate into fat, will both tend to raise the R.Q. Both factors are probably concerned in the abnormally high values found at the onset of hibernation.

Under certain circumstances a respiratory quotient of abnormally low value has been obtained, particularly at the end of hibernation. The meaning of this is not clear. It has been ascribed to a conversion of fat into glycogen, which is stored preparatory to awakening. It is doubtful, however, whether the amount of carbohydrate thus formed is sufficient to account for the retention of so much oxygen. Further, the low R.Q. may be due to other causes, as, for

instance, to incomplete oxidation evidenced by the appearance of lactic acid in the urine.

Factors Influencing the Expenditure of Energy

Food.—An important question has here to be settled. Does the rate of metabolism rest with the initiative of the cell or with the amount of food supplied? Can the cell only be made more active through causing a physiological need for enhanced activity, or can it also be made more active by feeding it? It was noted by Rubner that when a large amount of protein was given there occurred an increased liberation of heat. The same thing occurred after ingestion of carbohydrates and fats, but to a much less extent. The surplus energy thus liberated is called the **specific dynamic energy** of the food. The cell on being flooded with protein, which it is unable to store, is forced to burn it, quite irrespective of any demands for heat-production on the part of the body as a whole, and without any increase in voluntary activity. On the other hand, it may be that the presence of protein makes the cell burn carbohydrates and fats more rapidly.

There is clear evidence that the rate at which metabolism occurs is dependent upon certain chemical substances in the blood, particularly those elaborated by the thyroid gland. When this organ is hyper-active the metabolic processes are quickened, and when it is deficient or absent they are retarded.

External Temperature.—Metabolism is profoundly influenced by changes in the temperature of the atmosphere. This will be discussed more fully in connection with the regulation of body temperature.

Muscular activity—Basal Metabolism.—It is clear that in order to estimate the effect of activity upon metabolism we must first try to find the energy liberated when no work is being done. In theory this means when none of the organs in the body are doing any work—that is, are merely existing in a healthy state. This has been termed

the **true basal metabolism**. In practice the most complete rest attainable involves considerable activity of the heart and lungs. The minimum of activity which can be attained occurs when the body is at complete mental and physical rest, when no digestion or absorption of food is going on, and when loss of heat by radiation is at its minimum. This is usually taken as the **Basal** or **Standard Metabolism**. It has been estimated as 1 Calorie per kilogramme of body weight per hour, or about 1700 C. per diem, for a man of average weight and size. In different individuals it varies, not with the weight but with the area of body-surface.

The energy output of an average person doing sedentary work has been found by direct and indirect calorimetry to be about 2500 C. per diem. When hard manual work is performed this figure may be doubled. These results agree fairly well with the energy intake as estimated statistically from the amount of food supplied to large communities. From the figures thus obtained it appears that the average daily consumption of food corresponds in men to an intake of 2500 C. for sedentary workers, and 4000 C. for those employed in manual labour.

CHAPTER X

INTERMEDIATE METABOLISM

WE shall now take each class of foodstuff in turn, and after summarising the changes which it undergoes during digestion, follow the transformation which it undergoes between absorption and excretion. Such transformation will be found to involve any of the following—

1. Conversion of molecules not immediately required for consumption into storage forms.
2. Incorporation into the structure of the living cell.
3. Conversion of one form of foodstuff into another, as, for instance, proteins into carbohydrates.
4. Conversion of toxic into non-toxic bodies.
5. Breakdown changes preparatory to oxidation.
6. Oxidation itself.

1.—METHODS OF INVESTIGATION

Among the methods employed for investigating these intermediate reactions are the following:—

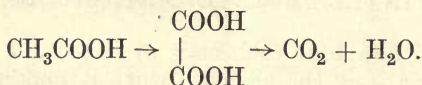
1. The *direct estimation* of substances in the blood, tissues and excretions.

2. *Administration of Intermediate Substances.*—A substance, A, given to the body is excreted in the form D. There are two substances, B and C, which might from a chemical point of view be intermediate stages in the change. B and C are injected into the animal. If B is excreted unchanged, and C is converted into D, the inference is drawn that the normal course of metabolism is $A \rightarrow C \rightarrow D$ rather than $A \rightarrow B \rightarrow D$.

Example : Acetic acid is completely oxidised in the body. Theoretically, either formic acid or oxalic acid might be an intermediate compound. But oxalic acid on injection is excreted unchanged, whereas formic acid is oxidised. The oxidation of acetic acid therefore takes place thus—



rather than thus—



3. *Administration in Excess.*—When a substance is injected in excess of the amount which can be completely oxidised it often appears in the urine in an incompletely oxidised form.

Example : Xanthine administered in small quantities to most animals is converted into allantoin. Administered in excess it appears partly as allantoin, partly as uric acid. Uric acid is therefore an intermediate stage.

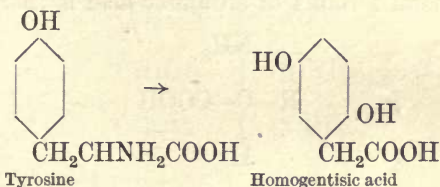
4. *Perfusion and Digestion with Tissue-Pulps.*—By this means have been proved the conversion of ammonia into urea by the liver and many other reactions.

5. *Pathological Method.*—When an abnormal substance, A, is excreted owing to a pathological condition, if the administration of a substance B, leads to increase in the amount of A, the inference is drawn that B is converted into A, and that the same change may occur under normal conditions, but is masked owing to the complete oxidation of A.

Example : Administration of certain amino-acids leads in diabetes to an increase in the amount of glucose excreted. The body therefore possesses the power of converting protein into carbohydrate.

An interesting instance of this method is found in the abnormality known as alcaptonuria. In this condition homogentisic acid is excreted by the kidney, and the corre-

spondence between the amount of this substance excreted and the amount of tyrosine ingested shows that these are related. It is therefore believed that tyrosine is, under normal circumstances, first changed into homogentisic acid, and that the alcaptonuric cannot oxidise homogentisic acid.



6. *Knoop's Resistant Radical Method*.—Substances which are readily oxidised under normal conditions are incompletely oxidised when they are linked to another substance itself resistant to oxidation. By linking fatty acids to the benzene ring important deductions can be drawn as to the normal metabolism of these acids (see p. 202).

The location of these changes in a particular organ can be made—

1. By the perfusion and digestion methods mentioned above.
2. By studying the effect of removal of the organ under investigation from the circulation.
3. By a comparative analysis of the blood entering and the blood leaving the organ.

2. PROTEINS

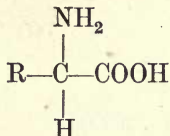
The Nature of Proteins

A protein is a substance containing carbon, hydrogen, oxygen, nitrogen, and sometimes sulphur and phosphorus. Structurally it consists of a large number of amino-acid molecules linked together by condensation. Into these

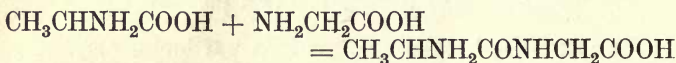
constituents it can be resolved by boiling with acids or by the action of certain ferments.

An **Amino-acid** is an organic acid in which a hydrogen atom, other than that of the carboxylic group, is replaced by an NH_2 group. In all the amino-acids occurring in nature, such substitution occurs in the α position.

The general formula of an amino-acid is therefore—



An amino-acid can be regarded not only as an acid containing an NH_2 group, but as a substituted ammonia. It is therefore an acid at one point and a base at another. For this reason the acid group of one amino-acid can, under certain circumstances, combine with the basic group of another, thus—



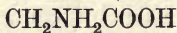
It will be observed that in this new compound there are still a COOH group and an NH_2 group intact. This process of condensation can therefore, theoretically, be continued indefinitely. The compounds thus formed are called di- tri- poly-peptides, according to the number of amino-acid molecules composing them. The most complex poly-peptide hitherto made artificially contains eighteen amino-acid molecules.

The following are the principal amino-acids:—

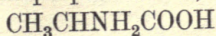
The Principal Amino-acids

I. *Aliphatic Series.*

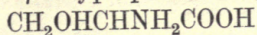
Glycine (amino-acetic acid)



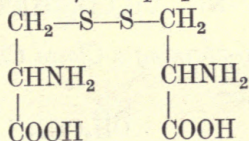
Alanine (α -amino-propionic acid)



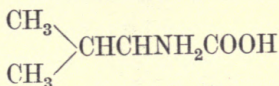
Serine (α -amino- β -oxypropionic acid)



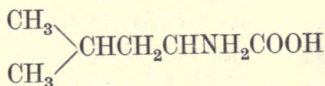
Cystine (Di- α -amino- β -thiopropionic acid)



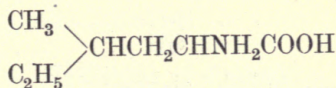
Valine



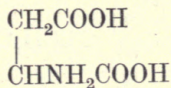
Leucine



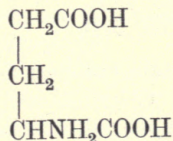
Isoleucine



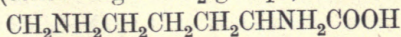
Aspartic acid



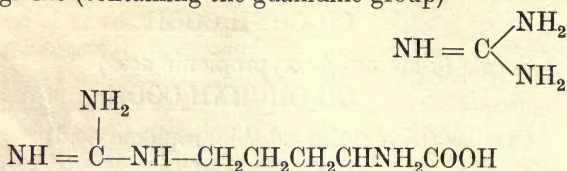
Glutamic acid



Lysine (containing 2 NH_2 groups)

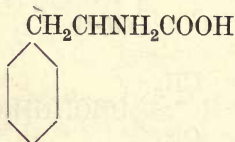


Arginine (containing the guanidine group)

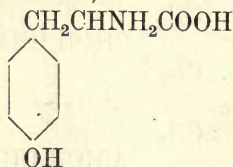


II. Amino-acids containing a Closed Chain.

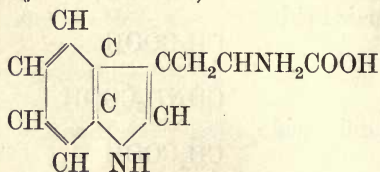
Phenyl alanine



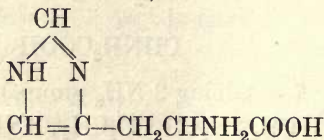
Tyrosine (oxyphenyl alanine)



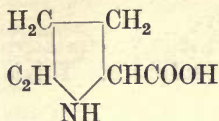
Tryptophane (β -indol alanine)



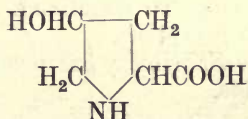
Histidine (β -imidazol alanine)



Proline



Oxyproline



Classification of Proteins

Proteins are divided into two main groups.

1. *Simple Proteins*, conforming to the definition of a protein given above. Such are fibrinogen of blood, myosin of muscle, casein of cheese. These are classified into sub-groups, *e. g.* albumins, globulins, etc., according to their solubility and precipitability by certain reagents.

2. *Conjugated Proteins*.—In these the protein molecule is linked with a non-protein molecule; with nucleic acid, for instance, in nucleo-proteins.

Hydrolysis of Proteins

In the breakdown of proteins to amino-acids certain intermediate stages are recognised. The disruption of the protein molecule is a gradual process, involving the successive subdivision of ever-shortening chains of amino-acids. The diminution in size of the molecules is accompanied by a physical change involving increase in solubility and decrease in precipitability.

The first recognisable change is that the molecule, if originally completely insoluble, becomes soluble in dilute acid or alkali, but the solution is easily precipitated and is coagulated by heat. In this stage it is called a **meta-protein**. It then becomes soluble in water, is not coagulated by heat, and requires half-saturation with ammonium

sulphate to precipitate it. It is now known as a **primary proteose or albumose**.

In the third stage it is precipitated only on full saturation with ammonium sulphate. This is a **secondary proteose or albumose**.

In the fourth stage the molecule is sufficiently small to diffuse through an animal membrane. It cannot be precipitated. This is a **peptone**.

In the fifth stage diffusibility has increased. The molecule is now a **polypeptide**.

The final stage is the separation into individual **amino-acids**.

It must be realised that, notwithstanding these stages, *the process is essentially a continuous one*, involving a gradual disintegration of the protein molecule. Further, the process takes place irregularly, so that at any stage molecules of different size are present.

The importance of recognising the above stages lies in the light thus thrown upon the action of the different proteolytic ferments.

Pepsin, acting only in presence of free hydrochloric acid, converts protein into a mixture of proteoses and peptones. **Trypsin**, acting in an alkaline medium, converts protein through all its stages into polypeptides and amino-acids, but it appears to be incapable of breaking down all polypeptides into amino-acids. **Erepsin**, also alkaline, has no action upon proteins, but converts peptones and polypeptides completely into amino-acids.

The succession of an acid by an alkaline digestion occurs not only in all animals, including even *Amoeba*, but also in insectivorous plants. It appears that certain protein linkages are more readily sundered by an alkaline ferment after other linkages have been broken by an acid ferment.

Absorption of Proteins

The proteins found in the various tissues differ from one another not in containing different amino-acids, but

in containing the same amino-acids combined in different proportions and in different ways. The individuality of a protein is due to the arrangement of the amino-acids of which it is composed. When animal proteins are being built from plant proteins the change consists in a rearrangement of amino-acids. Assuming that the animal body cannot to any extent synthesise amino-acids, it might be expected that such rearrangement must first involve breakdown of the food protein into its amino-acids, and the ample provision of the means of effecting this breakdown in the intestine would seem to confirm this view.

But until recently proof of this was wanting. It was difficult to detect amino-acids in the intestine owing, as we now know, to their rapid absorption, and still more difficult to detect them in the blood.

Four views were held.

1. That breakdown into amino-acids is not a necessary preliminary to absorption.
2. That amino-acid formation occurs only for the purpose of absorption, being followed by immediate resynthesis within the intestinal wall.
3. That amino-acids are absorbed, and after absorption are deaminised in the intestinal wall, ammonia and a non-nitrogenous residue being carried into the circulation.
4. That amino-acids are absorbed and circulate in the blood.

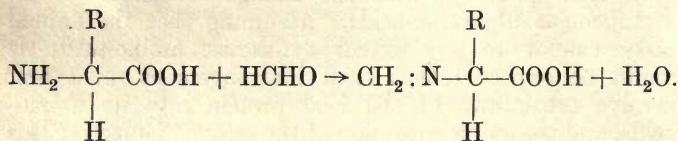
The first three theories may be dismissed, since they have been disproved by the positive evidence in favour of the fourth. This evidence is here presented.

1. *Abel's Vividiffusion Method (Artificial Kidney)*

This is a device for separating amino-acids from circulating blood. The blood is passed from the blood-vessel through a tube whose walls are made of collodion. This is immersed in a saline solution isotonic with blood. The blood is then returned to the circulation. The amino-acids readily diffuse through the collodion, and can be estimated.

2. Estimation of Amino-acids in Blood

Sørensen's method.—This depends upon the fact that amino-acids on treatment with aldehydes undergo this change.



The NH_2 group being thus destroyed, the resulting product behaves as a true acid and can be estimated by titration.

By the use of these methods it has been shown that the blood even in the fasting condition always contains amino-acids, (3–5 mg. per 100 c.c.), and the tissues from five to ten times as much as the blood. During protein digestion the amino-acid content rises in the general circulation, and rises still more in the portal vein. But at the same time there is no accumulation of amino-acids either in the liver or in the other tissues. As regards the liver, the amino-acids are evidently converted into some other form; they are either destroyed or synthesised into more complex bodies.

When a certain quantity of amino-acids is *injected* into the blood it rapidly disappears. Part is excreted by the kidneys either unchanged or as urea, but the remainder is absorbed by the tissues. In the liver there is a rapid rise, followed by a fall. In the other tissues the rise is more gradual and soon reaches a maximum, which is maintained for a considerable time. Simultaneously there is a rise in the urea of the blood, setting in before the tissues have become saturated with amino-acids.

Confirmatory evidence against the absorption of foreign proteins without preparatory hydrolysis is found in the remarkable reaction known as **anaphylaxis**. When a protein is injected into the blood

in two doses separated by an interval of about three weeks, immediately upon administration of the second dose the animal becomes collapsed and dies.

The Subsequent History of the Amino-Acids

Before considering the significance of the above facts it is necessary to trace the metabolism of nitrogen compounds from the other end—that is, from their elimination. Much light is thrown by a study of the effects upon nitrogen elimination on variations in the amount of protein absorbed. This is shown in the accompanying table.

	Nitrogen—rich diet.	Nitrogen—poor diet.
Volume of Urine	1170 c.c.	385 c.c.
Total Nitrogen	16·8 gms.	3·60 gms.
Urea Nitrogen. . . .	14·7 gms. = 87·5%	2·20 gms. = 61·7%
Ammonia Nitrogen . .	0·49 gms. = 3·0%	0·42 gms. = 11·3%
Uric Acid Nitrogen . .	0·18 gms. = 1·1%	0·09 gms. = 2·5%
Creatinine Nitrogen .	0·58 gms. = 3·6%	0·60 gms. = 17·2%
Undetermined Nitrogen .	0·85 gms. = 4·9%	0·27 gms. = 7·3%

(Folin).

It will be seen that while creatinine is almost unaffected by diet, urea undergoes a very considerable variation, the other urinary constituents occupying an intermediate position. These observations led Folin to distinguish two forms of nitrogen metabolism. In one form the amino-acids not required for tissue-building are split into ammonia and a nitrogen-free residue. The ammonia is converted into urea, and the non-nitrogenous part is burnt up like a carbohydrate or fat. This Folin termed “**exogenous metabolism.**” In the other form the amino-acids are taken up by the tissues and incorporated into the structure of the cell. Now since the cell is constantly

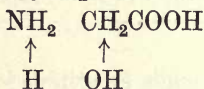
undergoing wear and tear, the amount of which must necessarily be determined by activity and not by diet, the nitrogen in the urine which originates in cell-breakdown must be that part which is not influenced by diet—that is, creatinine. This is “**endogenous metabolism.**”

The other constituents of urine—uric acid, ammonia and “undetermined nitrogen” (which chiefly consists of amino-acids and nitrogenous bases)—are partly of exogenous, partly of endogenous origin.

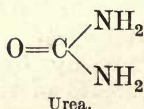
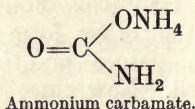
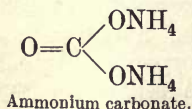
During starvation the amino-acid content of the blood is slightly increased. This is due to a breakdown of protein in the less essential organs, such as the skeletal muscles, and a transference of amino-acids to the indispensable organs, such as the heart and brain. Migration of amino-acid also occurs in fish during the spawning season. Here the nucleo-protein of the sexual organs is being built up at the expense of stored muscle protein (see p. 172).

The Formation of Urea

The amino group which is split off from the amino-acid in exogenous metabolism is converted into ammonia. This is probably effected by a process of hydrolysis:—

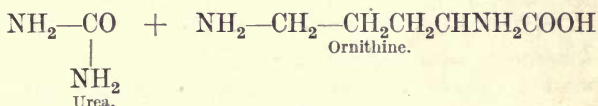
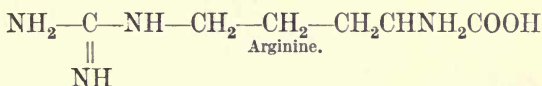


The ammonia thus liberated combines with any acid radicles which may be present in the blood. Carbonic acid being the most abundant of these, loose compounds are formed—ammonium carbonate and ammonium carbamate. The close relation which these two substances bear to one another and to urea is shown by their formulæ:—



While the process of deamination seems to occur in all living cells, the formation of urea occurs pre-eminently in the liver. Ammonium carbonate perfused through the liver is converted into urea. When in the living animal the liver is short-circuited by leading blood direct from the portal to the hepatic vein (Eck fistula) ammonia accumulates in the blood. But even under these circumstances urea formation does not cease. The liver, therefore, though the principal, is not the sole seat of the change.

A small amount of urea may be derived from **arginine**, the amino-acid which contains the guanidine group. Several tissues contain an enzyme, arginase, which has the power of splitting arginine into urea and ornithine.



The Excretion of Ammonia

When ammonia, split off from amino-acids, combines with an acid radicle other than CO_2 it is excreted as an ammonium salt. If it combines, for instance, with chlorine it is excreted as ammonium chloride. When abnormal acids accumulate in the blood as β -hydroxybutyric acid in diabetes, ammonium salts of these acids are formed and excreted. The ammonia may be said to be diverted from its normal metabolic path in order to neutralise the acids.

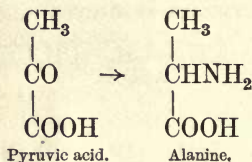
Synthesis and Inter-conversion of Amino-acids

Can the body synthesise amino-acids from ammonia and a non-nitrogenous group, and can it transform one amino-acid into another? These questions are of fundamental importance, for upon the answers to them depends the

protein requirement in diet. If the tissues cannot make amino-acids, but can only utilise for tissue-building purposes such amino-acids as are presented to them, then the form as well as the quantity of the protein in the food must be taken into account. But if the body can convert the nitrogen compounds presented to it into the amino-acids required for the specific structure of its tissues, then the quantity of protein is the sole consideration.

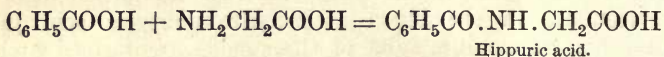
There is some indirect evidence that the body has the power of manufacturing amino-acids.

Synthesis of Alanine.—When the liver is perfused with pyruvic acid alanine is formed—



Alanine is also formed on perfusion of the liver with ammonia, provided that the liver is rich in glycogen. These facts point to a synthesis of alanine from ammonia and non-nitrogenous compounds.

Formation of Glycine.—Herbivorous animals daily excrete considerable quantities of *hippuric acid*. This is formed *in the kidney* by synthesis of the benzoic acid from the food with glycine.



Now the amount of glycine thus used is far greater than the amount which exists in the tissues and food. Glycine is therefore being formed in the body from more complex amino-acids.

There is also evidence that the body can effect the interconversion of histidine and arginine, and of tyrosine and phenylalanine.

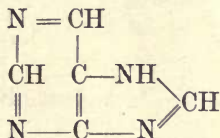
But the positive evidence for the synthesis of amino-

acids ends here. On the other hand, there is considerable evidence to show that for the more complex amino-acids animals depend upon plants. We shall consider this more fully in connection with nutrition, merely noting at this stage that the capacity of the animal body for synthesising amino-acids is limited to the very simplest of these. The possible conversion of amino-acids into compounds other than protein is discussed later (see pp. 190 and 201).

3.—PURINES

The purines form a group of closely related substances found extensively in living tissues. They may be regarded as composed of two urea groups united together through a central chain of three carbon atoms so as to form a double ring.

Purine, though itself only of theoretical importance, may be taken as a starting-point. It has the formula $C_5H_4N_4$, or

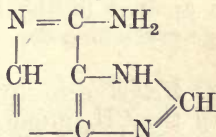


Its principal derivatives may be thus classified :—

1. *Amino derivatives* (with or without oxygen) :—

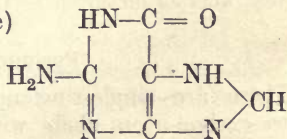
Adenine (amino-purine)

$C_5H_3N_4NH_2$ or



Guanine (amino-oxypurine)

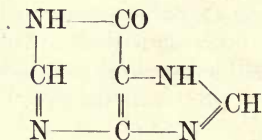
$C_5H_3N_4ONH_2$ or



These two substances form an essential constituent of nuclei.

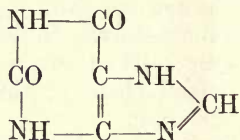
2. Oxidation products :—

Hypoxanthine (oxypurine)
 $C_5H_4N_4O$ or

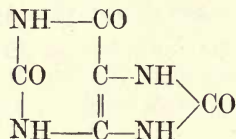


This occurs in all muscular tissue.

Xanthine (dioxypurine)
 $C_5H_4N_4O_2$ or



Uric acid (trioxypurine)
 $C_5H_4N_4O_3$ or



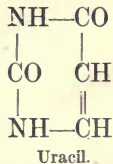
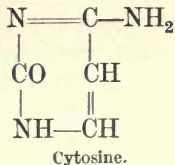
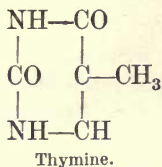
Uric acid is the form in which in man purines are excreted, the daily urine containing about 0.75 gm. It is also found in human blood (1–3 mg. per 100 c.c.). In gout the amount in the blood is considerably increased and large crystalline deposits are formed in the joints.

3. *Methyl derivatives*.—Purine bodies occur combined with the CH_3 group, as *caffeine* in coffee, as *theophylline* in tea, and as *theobromine* in cocoa.

Pyrimidine Bases

These are single-ring nitrogen bases consisting of a three-carbon-atom chain with *one* urea group.

Three are known :—

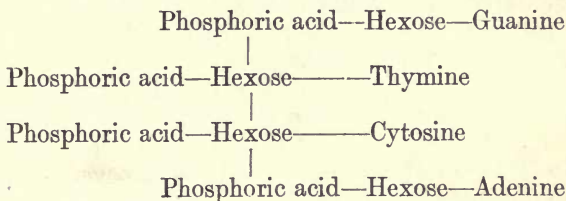


Of these, thymine and cytosine occur in animal tissues as components of nuclear material. Little is known of their metabolism. They can be synthesised in the body; they do not appear in the urine.

Nucleic Acid

Nuclear tissue consists of nucleo-protein—a protein conjugated with nucleic acid.

Nucleic acid as it occurs in animals is composed of four molecules of phosphoric acid, four of a hexose derivative and one molecule each of adenine, guanine, thymine and cytosine. These are believed to be combined in the following way :—



The combination, hexose + nitrogenous base, is termed a **nucleoside**, and the combination, phosphoric acid + hexose + nitrogenous base, a **mononucleotide**. Nucleic acid is therefore called a **tetranucleotide**.

Briefly, the problem before us is to correlate the purines taken in with the food, the amino-purines of nucleic acid, the hypoxanthine of muscle, and the purines excreted in the urine.

Physiological Synthesis of Purines

This is abundantly proved.

1. Salmon during the breeding season form large quantities of nucleic acid in the sexual organs, the heads of spermatozoa consisting almost entirely of this substance. Since during this period the fish take no food, the nucleic acid must be formed from the tissue proteins, chiefly the muscles.

2. Purines, absent from the newly laid egg, develop during incubation.

3. Mammals, both growing and adult, produce and excrete purines indefinitely when fed on milk or other purine-free diet.

Exogenous and Endogenous Purine

The amount of purine excreted depends upon the amount ingested. In man the urinary uric acid is increased after feeding with substances such as thymus which are rich in purine. When uric acid itself is administered it can be recovered in the urine, sometimes almost completely. From hypoxanthine and xanthine there is a yield of uric acid corresponding to about 50 per cent., and from adenine and guanine a smaller yield.

When no purines are present in the diet, uric acid continues to be excreted, being derived evidently from the purines of the body. The source of the uric acid excreted is therefore twofold, exogenous and endogenous.

Two questions now have to be considered.

1. How does the body transform the purines, whether from the food or from the tissues, into uric acid?

2. What conditions determine the conversion and excretion of body purines?

The Formation of Uric Acid from Nucleic Acid

Our knowledge of this subject has been obtained by studying the chemical changes which occur when nucleic

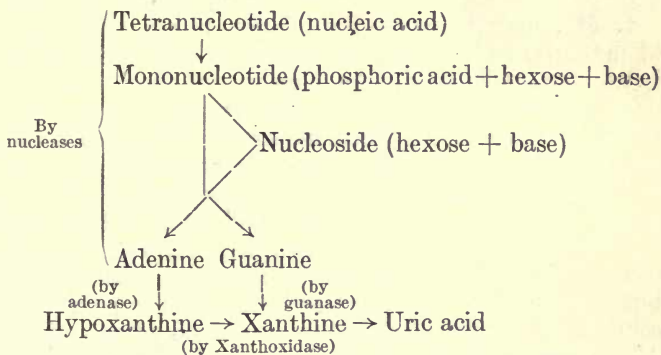
acid and purines are administered to the intact animal, when these substances are digested with various tissue extracts, and when tissues are allowed to undergo autolysis. Using these methods, the conversion of nucleic acid into uric acid has been ascribed to a series of enzymes. The change occurs in the following stages :—

1. By a series of ferments termed **nucleases**, the tetranucleotide is split into mononucleotides, from which are liberated adenine and guanine either directly or through the intermediate formation of nucleosides.

2. Deaminising ferments, **adenase** and **guanase**, convert respectively adenine into hypoxanthine and guanine into xanthine.

3. The ferment **xanthoxidase** oxidises hypoxanthine to xanthine and xanthine to uric acid.

These changes may be thus set forth :—



It is not to be imagined that all these ferments exist in every tissue. Indeed, their distribution appears to be limited to a few organs, such as the liver, pancreas and spleen, and even in these they are not all present. Wide

variations also occur according to age and species. It is worthy of notice here that gastric and pancreatic juice have no action upon nucleic acid, and that intestinal juice only converts it into the mononucleotide form. Nucleic acid is therefore absorbed practically unchanged. The conversion of nucleic acid into uric acid occurs almost entirely in the liver and spleen. It does not occur in the kidney.

The Formation of Uric Acid from Muscle Hypoxanthine

Hypoxanthine exists in muscle combined with hexose and phosphoric acid, forming inosinic acid. It is not derived from adenine, for muscle contains no adenase. The oxidation of muscle hypoxanthine to uric acid, supposing this to occur, must have its seat in the liver, for this is the only organ which contains xanthoxidase.

Factors Influencing the Formation of Endogenous Uric Acid

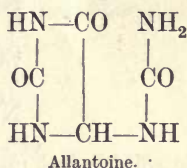
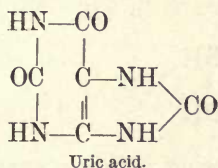
1. *Muscular Activity*.—The relation between the degree of muscular activity and the amount of uric acid excreted is not yet understood. An increase in purine excretion does not always follow muscular exercise. Some have found it to occur only when the exercise has been severe, or when the form of the exercise is unusual. It is said to follow involuntary muscular activity such as shivering rather than voluntary exercise, and tonic rather than repeated contraction. It has also been observed that the increase of uric acid excretion occurs not immediately but two or three days after exercise. The hypoxanthine content of muscle is said to be increased after activity. All we can say definitely is that muscular activity is not necessarily associated with a contemporaneous liberation of muscle purine.

2. *Fevers*.—The increased uric acid excretion which invariably accompanies fevers is to be ascribed to the abnormal breakdown of tissue, particularly of muscle.

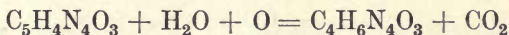
3. *Diet.*—A meal rich in proteins, though free from purines, leads to an increase in the excretion of uric acid which precedes the rise in urea excretion. Its causation is not clear. It may be derived from the digestive glands owing to their increased activity. It may be due to the metabolism of leucocytes, the numbers of which in the circulation are increased during digestion. The latter view is supported by the fact that in leucocythæmia, a pathological condition associated with a high leucocytosis, there is a considerable rise in purine excretion. On the other hand there is no quantitative relationship between the rise in uric acid excretion and the degree of leucocytosis.

Purine Metabolism in Animals other than Man

Man is almost unique among mammals in excreting uric acid as the principal end-product of purine metabolism. Other mammals, with the curious exception of the Dalmatian breed of dogs, carry purine metabolism one stage further—to **allantoine** :—



or



the allantoine being excreted by the kidneys.

The conversion of uric acid to allantoine is effected by the enzyme **uricase** or **uricolytic ferment**, which is found chiefly in the kidney and liver. This ferment is not present in man.

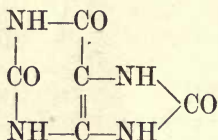
In birds uric acid forms the chief end-product not only of purine metabolism but also of protein metabolism in

general. In these animals it is the most abundant nitrogenous substance in the urine, urea being present only to a slight extent. When the liver is short-circuited by an *Eck fistula* the amount of uric acid excreted falls considerably, its place being taken both in the blood and in the urine by ammonium lactate. When an extract of avian liver is digested with ammonium lactate, uric acid is formed. In the bird, then, the liver synthesises uric acid, taking the three-carbon-atom chain from ammonium lactate.

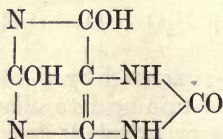
Gout

Our ignorance of the cause of gout arises largely out of the uncertainty which exists as to the form in which uric acid and its salts occur in the blood. Fresh blood contains more uric acid after boiling with acids than before. This suggests that some of the urates exist in combination.

It is said that the sodium salts exist in two forms, the *lactam* form, or α -urate—



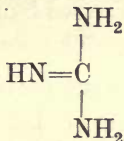
which is soluble but unstable, being readily converted into the *lactim* form, or β -urate—



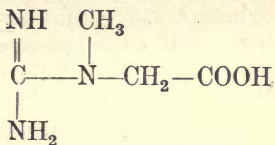
which is less soluble. It has been suggested that the formation of gouty deposits is due to the conversion of the soluble α - into the insoluble β - form.

4.—CREATINE AND CREATININE

These two substances contain the guanidine group—

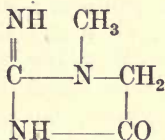


Creatine is methyl guanidine acetic acid—



It occurs in all tissues, but principally in skeletal muscle (0.4 per cent.). In normal adult urine it occurs only after a meat diet. It appears during starvation and in fevers. It is constantly present in the urine of children, and in the urine of women during pregnancy and menstruation.

Creatinine—



is a dehydration product of creatine which can be obtained by boiling creatine with acids. It occurs in normal urine, 1-2 grms. being excreted daily.

Effect of Administration

When creatine is given by the mouth some undergoes bacterial decomposition in the intestine, some appears in the urine partly as creatine, partly as creatinine, and some disappears.

When creatine is injected into rabbits the greater part appears unchanged in the urine, but some is deposited in the muscles and some is excreted as creatinine.

Creatinine when administered by mouth can be recovered almost completely in the urine.

Endogenous Creatinine

When an animal is fed on food free from these substances the daily excretion of creatinine attains a figure (for men about 0.6 grm., measured as nitrogen) which is remarkably constant, being influenced neither by diet nor by work. On this account the source of creatinine is ascribed to endogenous tissue metabolism, of the extent of which it therefore forms a measure. This view is supported by the greater excretion of creatinine during growth and during fevers.

Creatine of Muscle and Creatinine of Urine

The amount of endogenous creatinine excreted daily varies directly with the degree of muscular development—that is to say, with muscle mass. *Muscular work increases neither the creatine content of muscle nor the creatinine content of urine.* But a direct relationship has been established between creatine metabolism and **muscle tonus**. This is borne out by the following facts. Increased creatinine excretion has been found in soldiers to follow prolonged standing at attention, but not marching. Decreased creatinine excretion occurs during sleep. In artificially induced convulsions, which involve increase of tonus, there is an increase in the creatinine excreted and a decrease in the creatine of the muscles. Finally, the percentage of creatine in the uterus increases during pregnancy.

The appearance of creatine in adult urine seems to coincide to some extent with periods of muscle breakdown. It occurs, for instance, in wasting diseases and during the involution of the uterus following parturition. The evidence seems to show, therefore, that the creatinine

of the urine is related to the creatine of muscle, and that the latter is connected with the nutritional condition and not with the activity of muscular tissue.

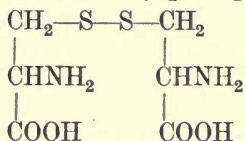
As regards the seat of formation of creatinine, the diminution in this substance found in most hepatic diseases points to its occurring in the liver. On the other hand, creatinine continues to be excreted after the establishment of an Eck fistula.

Concerning the substances from which creatine is formed we have no definite knowledge.

It will be seen that the significance of creatine and creatinine is far from clear. It is impossible in the present state of knowledge to state what part these substances play in metabolism.

5.—METABOLISM OF SULPHUR

Sulphur is taken into the body principally as **cystine**—



a constituent of most food proteins.

Sulphur is excreted in the urine in three forms :—

1. Inorganic sulphates.
2. The so-called “neutral sulphur”—an incompletely oxidised form the exact composition of which is unknown.
3. Ethereal sulphates.

It is also excreted in the bile as **taurine**, which enters into the formation of one of the bile-salts—sodium taurocholate.

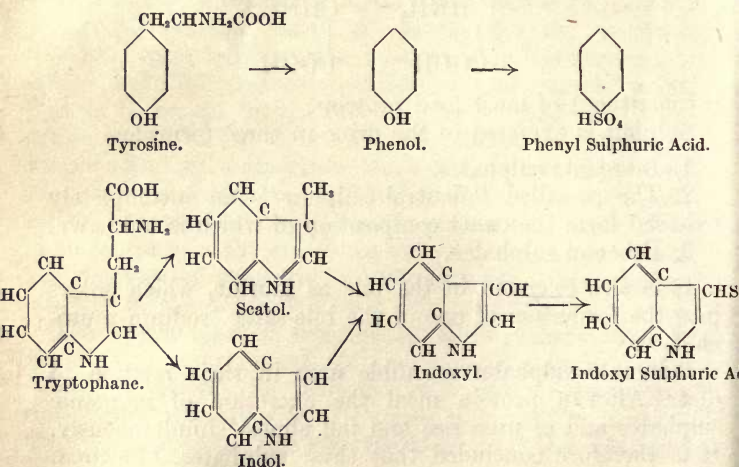
Inorganic sulphates resemble urea in their relation to diet. After a protein meal the excretion of inorganic sulphates and of urea rise and fall almost simultaneously. It is therefore concluded that these sulphates, like urea,

originate in the exogenous metabolism of protein. The cystine which is not required for tissue building, at the same time as it loses its NH_2 groups loses also its two sulphur atoms, which are oxidised and excreted.

The excretion of **neutral sulphur**, on the other hand, is hardly influenced by changes in diet. On this account it is considered to be of endogenous origin. The **ethereal sulphates** are salts of phenyl-sulphuric acid and indoxyl-sulphuric acid. They are formed in the following way:—

By bacterial decomposition in the intestine, and to a lesser extent in suppurating tissues, tyrosine and phenyl-alanine lose their side-chains and become converted into phenol. By the same process tryptophane becomes converted into scatol and indol. Phenol, scatol and indol, all toxic substances, are then absorbed into the blood. Within the body, probably in the liver, they become linked with sulphuric acid, phenol directly and scatol and indol after oxidation to indoxyl. The effect of this linkage is to deprive these substances of their toxicity prior to their excretion.

The above changes may be expressed thus:—



The potassium salt of indoxyl sulphuric acid is known as **indican**.

It follows from the origin of the ethereal sulphates that the extent to which they are excreted is a measure of the amount of intestinal putrefaction.

6.—CARBOHYDRATES

A carbohydrate is a substance containing carbon, hydrogen and oxygen, the hydrogen and oxygen being in the same proportions as in water.

The principal carbohydrates fall into the following groups :—

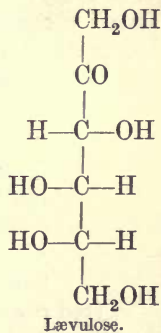
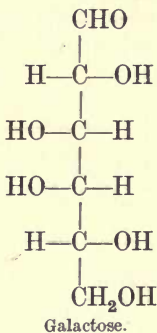
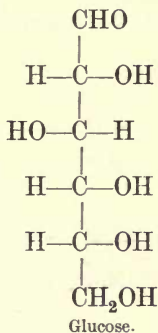
A. Monosaccharides or Hexoses ($C_6H_{12}O_6$).

Glucose (dextrose).

Lævulose (fructose).

Galactose.

The relation of these sugars to one another is seen from their formulæ.



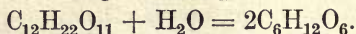
B. Disaccharides ($C_{12}H_{22}O_{11}$).

Cane sugar.

Maltose.

Lactose.

These on hydrolysis yield two molecules of a monosaccharide according to the equation—



Cane sugar yields glucose and lævulose.

Maltose yields two molecules of glucose.

Lactose yields glucose and galactose.

All the above sugars except lævulose are dextro-rotatory.

C. Polysaccharides ($\text{C}_6\text{H}_{10}\text{O}_5$).

These are substances of very high molecular weight. They include starch, inulin, cellulose, glycogen and dextrins.

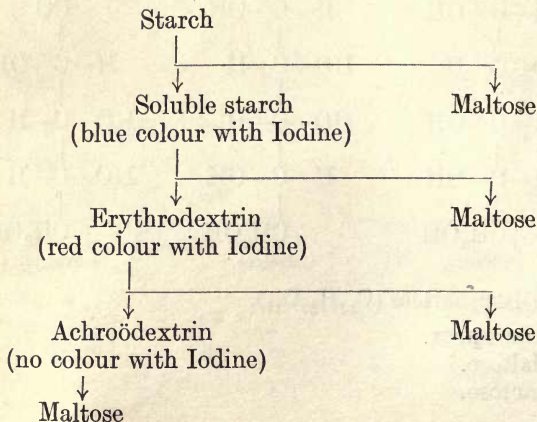
There exists also another series of sugars built up on a five-carbon-atom basis :—

Pentoses ($\text{C}_5\text{H}_{10}\text{O}_5$).

Pentosans ($\text{C}_5\text{H}_8\text{O}_4$) are the corresponding polysaccharides. They occur in vegetable foods.

Digestion of Carbohydrates

During digestion polysaccharides and disaccharides are converted into monosaccharides, the change in the case of starch occurring in the following stages, recognisable by the reaction with iodine :—



The conversion into maltose is effected by two ferments—**Ptyalin**, present in saliva, and **Amylase**, secreted by the pancreas. The disaccharides are hydrolysed by three ferments present in the succus entericus—maltose by **Maltase**, lactose by **Lactase**, and cane sugar by **Invertase** (so called because in the process the optical activity of the solution is inverted).

Metabolism of Carbohydrates

The only carbohydrates which can be absorbed by the intestine are the monosaccharides. Of these the most important is glucose. This sugar is the ultimate hydrolytic product of starch, cellulose and maltose, and it is a constituent of the disaccharides cane sugar and lactose. The glucose absorbed is practically all oxidised in the tissues to carbonic acid and water, the rate of oxidation being determined by the activity of the tissues.

Glucose, then, is being added to the blood intermittently from the intestine, and is being destroyed at a rate varying with the physiological activity of the body. Yet the amount of glucose in arterial blood remains fairly constant (0.10–0.15 per cent.). These facts indicate on the part of the body a considerable capacity for carbohydrate storage, and at the same time a mechanism for regulating a constant currency of glucose in the blood.

The Excretion of Sugar

Glucose occurs in normal urine to the extent of about 1 part in 1000—that is to say, in about the same concentration as in the blood. Such an amount, however, is not recognisable by the ordinary methods. When for any reason there is an increase in the blood-sugar (**Hyperglycæmia**) glucose appears in the urine (**Glycosuria**), but in a far higher concentration than in the blood. Assuming that the kidneys are acting normally, glycosuria indicates hyperglycæmia, though the amount of sugar in the urine is no measure of the amount of sugar in the blood.

Carbohydrate Storage—Glycogen

Our knowledge of this subject dates from the epoch-making researches of Claude Bernard (1855–1859). Bernard first showed that the blood in the hepatic vein contained sugar even after a flesh diet. This proved that the liver had the power of forming sugar. He then showed that when the liver was excised from a well-fed animal, the blood washed out and the organ rapidly plunged into boiling water so as to prevent any post-mortem change, there could be extracted from it a carbohydrate to which he gave the name of glycogen. If, however, he allowed the excised liver to remain at blood-temperature sugar began to form within it, and the glycogen at the same time diminished. Bernard believed that the interconversion of glycogen and glucose took place in both directions during life, and he was led to regard glucose as an internal secretion of the liver.

Glycogen is found, though not to the same extent as in the liver, in almost every tissue, chiefly in skeletal and cardiac muscle.

Glycogen is therefore the form in which carbohydrate storage occurs.

The Regulation of Carbohydrate Metabolism

We now have to consider the mechanism whereby the constancy of the blood-sugar is maintained although the rate of absorption and the rate of utilisation are independent of one another. It is clear that disturbance of this mechanism in the direction of hyperglycæmia, with coincident glycosuria, can be brought about in one of three possible ways. First, there may be a failure to convert ingested sugar into glycogen; secondly, there may be an abnormal flooding of the blood with sugar derived from glycogen; thirdly, the tissues may have lost the power of metabolising glucose.

We shall now discuss the conditions under which hyperglycæmia occurs, indicating as far as possible which of these three metabolic faults is responsible.

Alimentary Glycosuria

When carbohydrates are being digested and absorbed in large amounts, glycosuria follows. The maximum amount of any sugar which can be taken without causing glycosuria is known as the **Assimilation-limit** of that particular sugar. Considering that the rate of absorption must depend largely upon the degree of motility of the intestine, the amount of secretion and other variable factors, it is not surprising that the assimilation-limit should be subject to wide fluctuations. In spite of this, there are wide differences in the limit of different sugars. For glucose, for instance, it is about 200 grms., for lævulose 100–150 grms., for lactose 100 grms.

Alimentary glycosuria is in itself no indication of a profound disturbance of carbohydrate metabolism. Its occurrence merely signifies that the filtering capacity of the liver, if one may so put it, is overtaxed. But any material lowering of the assimilation-limit indicates an impairment of hepatic function.

Neurogenic Diabetes

In his search for a nervous influence over the secretion of sugar by the liver, Bernard discovered that glycosuria could be caused by injury to the *calamus scriptorius* in the floor of the fourth ventricle. This operation he called “diabetic puncture,” and the part of the brain so destroyed, *the diabetic centre*.

The efferent nervous path is *the splanchnic nerve*. Glycosuria can be excited reflexly by stimulation of the central end of the vagus and other nerves. Though it is clear from this that the sugar-forming function of the liver is under the control of the central nervous system, it is doubtful whether a diabetic centre in Bernard’s sense really exists. Glycosuria can be caused experimentally by injury to the cerebellum, and it occurs frequently in man after head injuries. Apart from trauma, glycosuria is

known to occur both in man and in lower animals when they are in a state of emotional excitement. Concerning this neurogenic form of glycosuria two points must be noted. First, that it is only transient; secondly, that it does not occur when the liver has been previously depleted of its store of glycogen. The fault therefore lies solely in an excessive discharge of glucose from the liver.

Before discussing further the manner in which the excessive production of glucose is brought about it is necessary to mention that glycosuria can be caused by **injection of adrenalin**. This complicates the problem considerably, for we have to decide whether the diabetes is due directly to the stimulation of the hepatic cells through the splanchnic nerve or indirectly to the coincident stimulation of the suprarenal glands.

Experiments on this point have led to conflicting results. By some observers it has been found that after removal of the suprarenals stimulation of the splanchnics fails to cause glycosuria; by others this has been denied. If, the suprarenals being intact, the hepatic branches of the splanchnics be cut and their peripheral ends stimulated glycosuria occurs, while the same experiment performed some time after excision of the glands causes only slight glycosuria. These experiments indicate that sympathetic excitation of the liver when the blood contains its normal amount of adrenalin is adequate to provoke the conversion of glycogen into glucose. When the splanchnics are stimulated after division of their hepatic branches only a slight degree of glycosuria occurs. We must therefore conclude that in this form of glycosuria two factors interplay—the direct action of the nerves upon the hepatic cells and the coincident stimulation of the suprarenal glands.

Pancreatic Diabetes

When the whole or nearly the whole of the pancreas is removed there follows a profound diabetic condition which

leads rapidly to death. If a part of the pancreas be grafted subcutaneously before the remainder of the gland is removed, diabetes does not occur, but it supervenes immediately upon the removal of the graft. This shows that the diabetic condition is due not to the nervous derangement incidental to such a severe operation, but to some chemical influence exerted by the gland through the blood-stream. The same fact is shown by the operation of *parabiosis*. This consists in making a crossed arterial connection between two animals so that their blood becomes mixed. Removal of the pancreas from one then causes diabetes in neither. When pancreatectomy occurs in pregnant animals diabetes is delayed until after parturition, indicating that the foetal pancreas influences the maternal blood.

The injection of blood from a depancreatized dog does not cause diabetes in a healthy animal. The pancreas therefore does not act by removing from the blood some disturbing element. Analysis of the liver in this condition shows that this organ has lost its power of forming and retaining glycogen. But more important than this is that the tissues *have lost the power of utilising glucose*. This is proved by the fact that on injecting glucose there is no rise in the respiratory quotient. The blood is therefore flooded with sugar, which leaves it only through the kidneys. Concerning the nature of the pancreatic influence upon the glycolytic powers of the tissues nothing definite is known.

So far we have seen that the rate of formation of glucose by the liver is subject to nervous influences and to the condition of the suprarenal glands, and that the presence of the pancreas in the circulation is necessary both to restrain glucose formation in the liver and to promote glucose utilisation in the tissues. How far do these facts furnish a reply to the question from which we started,

namely, how is carbohydrate metabolism normally regulated? If the tissues, principally the muscles, require an amount of sugar which varies with their activity, and if the output of sugar from the liver is subject to nervous and chemical influences, there must be some mechanism for adjusting the supply to the demand. The hyperglycæmia which is caused by emotional conditions may be regarded as a mobilisation of sugar in anticipation of the muscular efforts of offence or defence which will be demanded of the animal by the cause of the emotion. But how is the carbohydrate supply increased to meet a demand unaccompanied by any emotional state, as in ordinary exercise? There are several ways in which the muscles may influence the liver to satisfy their needs:—

1. The path may be nervous throughout, originating in the afferent nerve-endings of the muscles and reaching the liver by the sympathetic. The only evidence suggesting such a mechanism is the reflex production of hyperglycæmia above noted.

2. Changes in the composition of the blood may affect the central nervous system, and this in turn the liver.

3. Changes in the composition of the blood may have a direct chemical effect upon the hepatic cells.

4. The effect upon the liver may occur only through an increased output of adrenalin, which may be caused either reflexly or by changes in the blood.

Experiments, so far as they go, indicate that several of these factors co-operate. Glycosuria, as we have seen, can be produced reflexly by stimulation of afferent nerves. As regards changes in the composition of the blood, these may be of two kinds—a diminution in the amount of sugar or an increased H. ion concentration. So far there is no evidence that diminished sugar content has any influence upon the liver. On the other hand, increased sugar output has been observed to follow an increased H. ion concentration, as after severe hæmorrhage. Since

this is not accompanied by increased adrenalin output it must be a direct effect upon the liver. But when the muscular exertion is sufficiently intense to cause cerebral anæmia increased output of adrenalin may occur, the suprarenals thus playing a supplementary part in sugar mobilisation.

Phloridzin Diabetes

Phloridzin, a substance obtained from the roots of certain trees, causes glycosuria on injection. The glycosuria, however, differs from those above described in that it is not accompanied by hyperglycæmia. It is evidently produced by a change in the permeability of the kidneys to sugar. The renal origin of the condition is easily proved. When the drug is injected into a renal artery glucose is excreted from the corresponding kidney earlier than from the opposite side. In spite of continued drainage the percentage of sugar in the blood remains normal or nearly normal. The need for making up in the blood the amount of sugar lost through the kidneys leads to a disturbance of carbohydrate storage and formation. The importance of phloridzin diabetes therefore lies in the light which it throws upon the capacity of the organism to produce sugar.

Human Diabetes

The low respiratory quotient observed in diabetics shows that this condition is due essentially to a loss of the power of glycolysis by the tissues generally. Hyperglycæmia is always present. The association of the disease with degenerative changes in the pancreas was early noted, and indeed was the cause of investigations into the influence of that gland upon carbohydrate metabolism. Whether the pancreas is always at fault is not known. It may be that pathological changes occur not visible on post-mortem examination. As to the location of the cause of the disease in the *Islets of Langerhans*, it has been found that

when the pancreas is incompletely extirpated the islets show signs of hyperactivity when diabetes does not occur, and degeneration without corresponding changes in the other tissue when diabetes supervenes.

The Formation of Glucose and Glycogen

In order to find out what substances are capable of forming glycogen three methods are employed. The substance in question may (1) be perfused through the excised liver, (2) be administered to the animal after the hepatic glycogen store has been exhausted by strychnine convulsions, (3) be administered to an animal rendered diabetic by extirpation of the pancreas or by administration of phloridzin. If in the last case the sugar excretion is increased it is concluded that the substance normally undergoes conversion into glycogen.

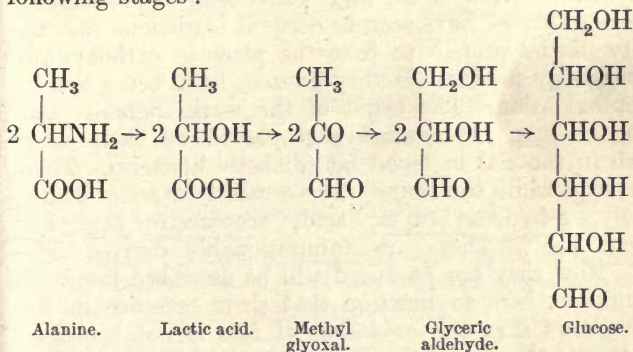
Using these methods the following information has been obtained :—

From Carbohydrates.—Glycogen is formed not only from glucose but also from lævulose, galactose, the ordinary disaccharides and from starch and cellulose; also from formaldehyde and from lactic acid. It is not formed from the pentoses or from the six-carbon-atom alcohols and acids, such as glycuronic acid.

From Proteins.—In the diabetic condition there is a constant ratio between the amount of glucose and nitrogen excreted. This is called the **D : N ratio**. When protein food is administered the excretion of glucose is increased. In some cases as much as 58 grms. of glucose can be obtained after ingestion of 100 grms. of protein. The production of carbohydrate from protein is therefore proved.

As to the individual amino-acids which can be converted into carbohydrate, it might be imagined that *glucosamine*, which contains the glucose molecule preformed, would be the principal source. But this is unlikely, first, because glucosamine forms only a very small part of the commoner proteins; secondly, because when given to the diabetic it

yields less glucose than does casein, from which this amino-acid is absent. Of the other amino-acids, several, including glycine, alanine, aspartic acid and glutamic acid, have been proved to be sources of glucose. The chemical changes involved are sometimes very complicated. There is good reason to believe that in some cases methyl-glyoxal, $\text{CH}_3\text{CO}\cdot\text{CHO}$, is formed as an intermediate compound. There exist in various tissues ferments, called glyoxylases, which transform methyl-glyoxal into lactic acid, the reaction being reversible. Methyl-glyoxal yields glucose in the diabetic organism, glyceric aldehyde being probably an intermediate compound, for this also is a source of glucose under the same conditions. Taking alanine as an example, it is probable that the change takes place in the following stages:—



The conversion of protein into sugar appears to take place not only in the liver but in the tissues generally, for it occurs after the liver has been short-circuited by an Eck fistula.

From Fats.—Either component of a fat, glycerine or the fatty acid might conceivably form a source of carbohydrate. Although the conversion of glycerine into glucose is not difficult to perform *in vitro*, it has been consistently found impossible to increase the excretion of glucose by admin-

istration of fats. On the other hand, in some cases of diabetes when there is no carbohydrate in the diet the D.N. ratio is higher than can be accounted for by the production of sugar from protein alone. This points to sugar production from fats. Though the evidence is inconclusive, it seems that sugar is produced from fat to a far less extent than from protein.

Further Metabolic Changes in Diabetes

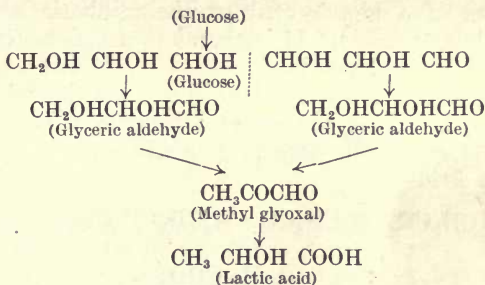
Notwithstanding the inability of the tissues to burn glucose, there is in the diabetic no decrease in the total metabolism or energy production of the body. The source of energy must therefore be transferred to the proteins or the fats. This is further shown by the low respiratory quotient. In view of the large conversion of protein into glucose which we have seen to occur it is obvious that the ability of the protein to take the place of carbohydrate as an energy producer is very limited, little being left for direct oxidation. The brunt of the work therefore falls upon the fats, the exalted part played by them being shown in the rise in blood fat (diabetic lipæmia). There soon appear in the urine the so-called acetone bodies, namely, β -hydroxybutyric acid, acetoacetic acid and acetone itself. These are unquestionably derived from fats. How they are produced will be described later. It is sufficient here to mention that their presence in the urine shows that the oxidation of fats is not complete. The tissues therefore either have a diminished capacity for fat combustion or are unable to cope with the increased fat oxidation consequent upon the failure to use proteins and carbohydrates. The accumulation of acetone bodies in the blood is indeed the usual cause of death in diabetics, for these substances have a toxic effect upon the nervous system. To some extent the body protects itself from this accumulation of acids in the blood by combining the acids with ammonia, which is thus deviated from its normal conversion into urea.

*4 carbon residue can't be oxidized
- acetone bodies \rightarrow death*

The Breakdown of Glucose

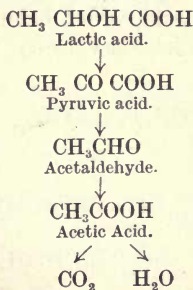
Though there are several ways in which glucose oxidation can theoretically take place, it is most probable that the molecule first splits into two molecules, each containing three carbon atoms. These eventually become converted into lactic acid. Lactic acid can be produced by the action of alkalis on glucose; it is formed in the body when the oxygen supply is inadequate; it is formed on perfusion of a liver loaded with glycogen; when given to the normal animal it yields glycogen, and when given to the diabetic animal, glucose.

The intermediate steps between glucose and lactic acid may probably be represented in this way:—



Each of the above changes can be produced *in vitro*. Glycerine (though not glyceric aldehyde) when perfused through the liver yields lactic acid.

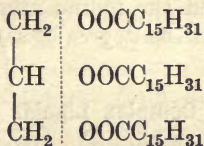
The further oxidation of lactic acid occurs probably through the intermediate formation of pyruvic acid, acetaldehyde and acetic acid.



It is now known that alcohol is not a usual intermediate compound.

ration, such as those of the linoleic series, $C_nH_{(2n-3)}COOH$, and the linolenic series, $C_nH_{(2n-5)}COOH$.

As an example of the constitution of a fat we may give glycerine tripalmitate :—

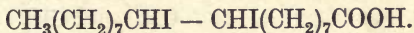


On boiling with alkalis (*saponification*) fats are hydrolysed, cleavage occurring, at the dotted line above, into glycerine and the sodium or potassium salt of the fatty acids (soap).

Saturated and unsaturated fatty acids differ from one another physically and chemically, the most important differences being—

1. **The Melting-point.**—Palmitic and stearic acids are solid at 60° , while oleic acid is liquid at 0° . When the fatty acid is combined with glycerine to form a fat it impresses upon that fat a melting-point which approaches its own.

2. **Behaviour to the Halogens.**—Unsaturated acids readily combine with the halogens, forming saturated compounds. Oleic acid, for instance, with iodine forms—



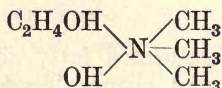
Since the iodine can be introduced at every double linkage, the amount of iodine thus taken up forms a measure of the degree of unsaturation of the acid; and since the double linkage remains unaffected in the synthesis of a fatty acid with glycerine, the resulting fat will absorb the same amount of iodine as the fatty acid of which it is composed. The amount of iodine with which a fat can combine is called its **iodine number**.

Fats as they occur in the body are mixtures of different

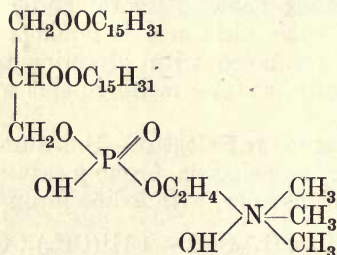
triglycerides, and since the properties of each triglyceride depend upon its fatty acid constituent, the properties of a mixed fat depend upon the proportion in which saturated and unsaturated fatty acids are present. So by estimating the melting-point and the iodine number of a mixed fat we have a measure of the degree of saturation of the fatty acids composing it.

Complex Lipoids

Phosphatides (Phospholipines).—These may be regarded as fats in which one fatty acid molecule is replaced by phosphoric acid, by means of which it is linked to the base **Choline**—



The most important member of this series is **Lecithin**—



Lecithin and allied substances form a constituent of all living cells.

Cerebrosides (Galactolipines) are compounds of fatty acids with nitrogen and galactose. They occur largely in nervous tissue.

Lipoids may therefore be said to exist in the body in two forms, as simple triglycerides and as more complex bodies.

Between these forms there is an important histological difference. The fats which are visible to the naked eye, or are visible in globular form through the microscope, and stain with the usual reagents are the triglycerides. They are the fats of ordinary adipose tissue. The complex fats, such as lecithin, are not visible microscopically, do not stain in the usual way, but under certain pathological conditions glycerides may separate out from the complex fats, and form globules which stain in the characteristic manner.

It is sometimes necessary to find out in any tissue how much of the lipid substance exists as triglyceride and how much in the complex form. This is done by estimating the proportion of fatty acid to the total lipid. Comparison of the formulæ given above for glycerine tripalmitate and for lecithin shows that the fatty acid constituent accounts in the former for about 95 per cent. and in the latter for about 60 per cent. of the whole molecule.

Absorption of Fat

Fat exists in blood in the form of ultra-microscopic particles—the *blood-dust*. Its amount is increased after a fat-rich meal. The greater part of the fat enters the blood through the lacteals and thoracic duct. When the thoracic duct is ligatured, fat continues to leave the intestine, though no demonstrable increase can be found in the systemic circulation. The fat is evidently transported from the intestine and deposited elsewhere with great rapidity. The site of such deposit appears to be the liver, for when fat absorption is in progress the fat in the portal vein exceeds that in the jugular vein.

In spite of the appearance of fat droplets within the intestinal epithelium, there is overwhelming evidence to show that fat is only absorbed after saponification into soaps and glycerine, and that these, after passing through the epithelium, are resynthesised. The evidence in favour of this view is as follows :—

1. There would be no reason for the existence of pancreatic lipase if such saponification were not necessary.

2. When a mixed emulsion of fats and hydrocarbon oils, such as turpentine, is introduced into the intestine fats only are absorbed. For absorption, therefore, something more than division into a fine particulate state is necessary. The substance must go into solution, and this in the case of fats can only occur by saponification.

3. When fats are introduced into the intestine they appear in the chyle as neutral fats. Synthesis with glycerine from some source unknown has therefore occurred in the intestinal wall.

4. Certain esters introduced into the intestine appear in the thoracic duct modified as regards both their basic and their acid constituents. Such a change could only occur after saponification.

The strongest evidence for the theory that fats may be absorbed as such is the fact that when fats are administered stained they appear stained in the thoracic duct. But this is due to the stains being soluble in the soaps.

The evidence therefore points to a saponification preceding and resynthesis succeeding absorption. Whether the two changes are brought about by different ferments or by the same ferment acting reversibly according to the laws of mass action we do not know.

The same problem occurs in the passage of fats between the blood and the cell for the purpose of storage or combustion. If such a transference necessitates saponification we must assume the ubiquitous existence of lipolytic and lipogenic enzymes.

The existence of fat in the body may be discussed under three headings.

1. *The Fat Depots.*—These are principally the subcutaneous tissues, omentum and peritoneum. The high percentage of fatty acid (95 per cent.) indicates that the fat exists in the form of simple triglycerides. Its low iodine number shows the high proportion of saturated fatty acids.

The character of the depot fat is easily influenced by the kind of fat in the diet. In dogs fed on mutton fat, for instance, the depot fat approaches mutton fat in type. This would seem to show that transformation of food fat into a particular kind of body fat within the intestinal wall does not normally take place to any appreciable extent, and that the character of the depot fat is an average of that of the fats eaten; there being normally very little change of diet, the character of the depot fat remains fairly uniform.

2. *The Tissue Fat.*—By this is meant the fat which is built up into the structure of the living cell, and not that which is found filling up the spaces in every tissue. The latter is only a form of depot fat. Tissue fat differs from depot fat in two respects. First, the fatty acids form only 65 per cent. of the molecule, suggesting that they are built up into a complex molecule, such as lecithin. Secondly, it has a high iodine value, indicating a high percentage of unsaturated fatty acids. The characteristics of tissue fat do not vary with the diet.

3. *The Liver Fat.*—The liver contains a higher proportion of fat than any other organ, in man as much as 70 per cent. of the dry substance being fatty acid. Under ordinary conditions the liver fat resembles tissue fat in having a high iodine value and a low percentage of fatty acid; the fat is therefore in the form of a lecithin. But after the ingestion of a considerable amount of fat of low iodine value, the liver fat assumes a low iodine value, this change preceding the similar change which occurs in the depot fat. Fat after absorption, therefore, is first deposited in the liver.

In the condition known as *fatty infiltration* there is a deposit of fat in visible triglyceride form in the hepatic cells. This occurs naturally during pregnancy and lactation, and pathologically in diabetes and after poisoning with chloroform or phosphorus. The fat deposited comes not from the complex lipoids of the liver but from the fat

depots. This is proved by the following experiment. Two dogs are fed, one of them on an ordinary diet, the other on linseed oil. On poisoning them with phosphorus the liver fat is found to be composed, in the former, of ordinary depot fat of the dog; in the latter, of linseed oil. The origin of the liver fat is therefore from the intestine and from the depots. Arrived at the liver, the fat undergoes two changes: *double linkages are introduced (desaturation)*, whether the fatty acids were previously saturated or unsaturated. Thus there are formed fatty acids still more unsaturated than oleic acid. The other change consists in the *building up of the fat into lecithin*, indicated by the fall in the proportion of fatty acid.

In other words, the liver converts the fat from the form in which it exists in the food and in the depots into the form in which it exists in the living cell. From this it would appear that the liver prepares the fat for use in the tissues, fat being more easily burnt after being desaturated. The process of desaturation also occurs in the tissues in general, but to a less extent than in the liver.

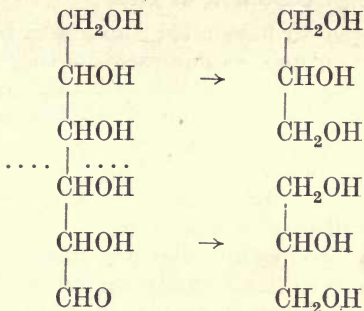
Formation of Fat from Carbohydrate

Though the conversion of carbohydrate into fat in the body must have been believed in for centuries, it was not until 1852 that it was actually proved. In that year *Lawes and Gilbert* took two pigs of similar size and weight from the same litter. One they killed, and estimated the fat, protein and carbohydrate content of its body. The other they fed on a diet of known composition. After a few months this pig was killed and analysed. The amount of fat present in this animal over and above that which was present in the animal killed earlier was found to be far in excess of the maximum which could theoretically have been derived from the fat and protein of the food.

A second proof of the conversion of carbohydrate into fat is alleged from the study of the respiratory quotient. In the early stage of hibernation the respiratory quotient

risks to an abnormally high figure (1.2–1.3). Assuming that there is not an abnormal retention of CO_2 in the body, this can only be explained by supposing that carbohydrates are being converted into fat, and that in the transformation a certain amount of oxygen becomes available for oxidation (p. 152).

The formation of glycerine from carbohydrate must be a very simple matter, as will be seen by a comparison of the formulæ:—



But as regards the fatty acids the question is more difficult. It is probable that the carbohydrate is first broken down into simpler compounds, such as acetaldehyde, CH_3CHO , and pyruvic acid, $\text{CH}_3\text{COCO}_2\text{H}$, and that the fatty acids are built up from these.

Formation of Fat from Protein

The evidence for the formation of fat from protein based upon a study of fatty infiltration and degeneration, is now known to be fallacious. We have already seen that fatty infiltration is due to mobilisation of fat from the depots. In fatty degeneration, such as occurs in the heart after diphtheria or in peripheral nerves after separation from the nerve-cell, there is a deposit of fat from the tissue itself. This, however, is not derived from protein, but is an unmasking of the fat from lecithin.

We have, indeed, no direct evidence of the transformation of protein into fat, except the fact that some amino-acids yield β -oxybutyric acid on administration to the diabetic animal. But we know that protein can be converted into carbohydrate and that carbohydrate can be converted into fat. There is therefore no reason why protein should not indirectly be converted into fat whenever fat is being rapidly laid down.

Oxidation of Fats

The first step, as we have seen, appears to be an introduction of double linkages, forming acids of the unsaturated series. It is now universally believed that oxidation of fatty acids occurs in the β -position—that is to say, that the carbon atoms in the chain (and they are always straight chains) are split off two at a time. This is the evidence:—

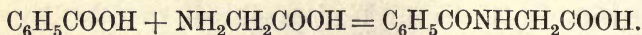
1. In animal fats only those fatty acids occur which have an even number of carbon atoms.

2. In butter all the even series are present from those containing eighteen to those containing four carbon atoms.

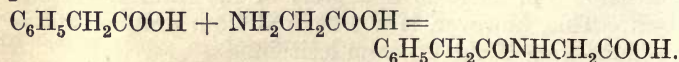
3. When fats are burnt incompletely, as in diabetes, we can detect substances partially oxidised in the β -position: β -hydroxybutyric acid, $\text{CH}_3\text{CHOHCH}_2\text{COOH}$, and acetoacetic acid, $\text{CH}_3\text{COCH}_2\text{COOH}$.

4. On perfusion of the liver with various fatty acids the formation of acetoacetic acid occurs only when the fatty acids have an even number of carbon atoms.

5. *Knoop's Experiment*.—When benzoic acid is administered it is excreted combined with glycine in the form of hippuric acid—



When the next homologue, phenyl-acetic acid, is given, this, too, is combined with glycine, with formation of phenaceturic acid—

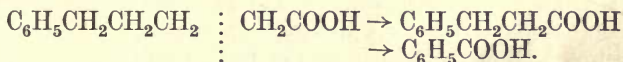


Continuing up the series, phenyl-propionic acid is excreted as hippuric acid, showing that two atoms of carbon have first been split off and benzoic acid formed.

The next member of the series, phenyl-butyric acid, is excreted as phenaceturic acid, showing that it has first been oxidised to phenyl-acetic acid. And so on alternately. These facts may be tabulated thus :—

	<i>Acid fed.</i>	<i>Oxidised to</i>	<i>Excreted as.</i>
Benzoic . . .	$\text{C}_6\text{H}_5\text{OOH}$	(not oxidised)	$\text{C}_6\text{H}_5\text{CONHCH}_2\text{COOH}$
Phenyl acetic .	$\text{C}_6\text{H}_5\text{CH}_2\text{COOH}$	(not oxidised)	$\text{C}_6\text{H}_5\text{CH}_2\text{CONHCH}_2\text{COOH}$
Phenyl propionic .	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COOH}$	$\text{C}_6\text{H}_5\text{COOH}$	$\text{C}_6\text{H}_5\text{CONHCH}_2\text{COOH}$
Phenyl butyric .	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$	$\text{C}_6\text{H}_5\text{CH}_2\text{COOH}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CONHCH}_2\text{COOH}$
Phenyl valeric .	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$	$\text{C}_6\text{H}_5\text{COOH}$	$\text{C}_6\text{H}_5\text{CONHCH}_2\text{COOH}$

It will be seen that the number of carbon atoms split off is always even. Phenyl valeric acid would appear to be oxidised thus :—

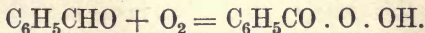


As to the oxidation of the two-carbon-atom chain we have no certain information.

8.—THE OXIDATION PROCESS

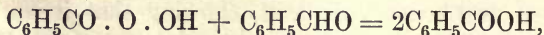
The nature of the oxidation of the foodstuffs is not yet completely elucidated. How are substances such as fats, which normally are so difficult of oxidation at body temperature, oxidised so easily in the tissues? Why, under certain circumstances, can some foods be oxidised and not others, as in diabetes?

It is believed that the oxygen must first be converted into atomic form through the formation of certain peroxides. A large number of substances, including aldehydes, carbohydrates, etc., undergo on exposure to oxygen at ordinary temperature slow oxidation, with intermediate formation of peroxides. An example is seen in the case of benzaldehyde—

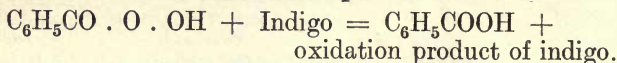


Benzoyl hydrogen peroxide.

Now the peroxide can, in undergoing further oxidation, impart an atom of oxygen to any substance which is capable of oxidation. This may be either another molecule of benzaldehyde—



or any other oxidisable substance present—



It is believed, therefore, that the cell contains peroxides which act like benzaldehyde in the above reaction, taking up molecular oxygen and imparting it to the food molecules as atomic oxygen.

This view is borne out by the close similarity which exists between the oxidation processes which take place in the body and those which occur *in vitro* by the action of the simplest peroxide, hydrogen peroxide. To give an example. Butyric acid is in the body oxidised to aceto-acetic acid. The only agent capable of effecting the same change outside the body is hydrogen peroxide. But it cannot be hydrogen peroxide itself which is responsible for oxidation in the tissues: first, because this substance is toxic; secondly, because several tissues contain a ferment **catalase**, which decomposes it with liberation of oxygen in molecular and therefore inactive form.

The transference of atomic oxygen from the peroxide to the substance undergoing oxidation is effected by means of enzymes called **peroxidases**. The existence of such enzymes has been demonstrated in certain vegetable tissues.

Hydrogen peroxide alone has a very slow oxidising effect on lactic acid, but in the presence of the living cells of the horse-radish oxygen is rapidly transferred from the H_2O_2 and oxidises the lactic acid. Now a similar acceleration occurs in the presence of traces of ferrous or manganese salts. For this reason, and also because either iron or manganese is nearly always found in the ash of peroxidases,

the view is held by some that peroxidases consist of these metals in colloidal form.

Peroxide and peroxidase form together a system known as an **oxygenase**. The failure of oxidation of certain substances which sometimes occurs can only be explained by supposing that different oxygenases exist for different substances, the specificity applying to either component of the system or to both.

CHAPTER XI

NUTRITION

THE choice of a diet is primarily a question of instinct. But instinct, while it can be trusted to provide a sufficiency in amount, may err in providing too much or in not providing a sufficiency in kind. In order that the diet may be adequate for the proper performance of the bodily functions, it must be sufficient in amount as a source of energy, and in kind as containing in proper amount all those substances which are necessary for the maintenance of the body structure and which cannot be synthesised in the body. The best diet is that which fulfils these functions with the most economical working of the digestive apparatus.

THE CARBON BALANCE

Assuming that the food is of such a nature as to provide adequately for the maintenance of the machine, we can inquire as to the amount and form in which it is best suited as a source of energy. As to the amount, this can be determined by comparing the carbon taken in as food and the carbon excreted. If these are equal the individual is in a condition of carbon balance, and the food is sufficient as a source of energy. If intake is in excess of output the energy supply is more than sufficient and storage is taking place. If output is in excess of intake the food is insufficient and the body is living upon the stores previously accumulated or upon the tissues themselves.

The following figures may be taken as showing the amounts of the three main classes of foods habitually eaten,

the lower figures applying to sedentary, the higher to manual workers :—

Carbohydrate	370–570 grms.
Fat	50–100 „
Protein	120–150 „

Since all three classes serve as a source of energy, the question arises as to what extent each of these is necessary. In view of the considerable powers possessed by the body of converting one form into another, it might be thought that each could to a large extent be replaced by either of the others.

The Carbohydrate Requirement.—We have seen how the body always maintains a constant sugar content of the blood; how when need arises, as in phloridzin diabetes, it transfers proteins into carbohydrates. When carbohydrates are withheld from the diet there follows a profound disturbance of metabolism, due to incomplete oxidation of fat. Carbohydrate, as such, is therefore a necessary component of the diet, but the minimum amount necessary is not known.

The Fat Requirement.—When fats are absent from the food, evidence of malnutrition soon appears, due, as we now know, not to a lack of fat as fuel, but of certain substances present in fat which act in some way other than as energy producers. Whether the body can live without fat as a source of energy is not yet determined.

The contraction of isolated muscle can be carried to the point of fatigue without any depletion of the fat present in the muscle. But this may be due to the absence of the circulation; there may be wanting some hormone necessary for the preparation of the fat for the furnace.

The oxidation of fat occurs normally without intermediate conversion into carbohydrate. This indicates that in the living cell carbohydrates and fats are being oxidised together.

THE PROTEIN REQUIREMENT—NITROGEN BALANCE

Protein cannot be considered merely as a source of energy owing to the important part which it plays in maintaining the body structure. The adequacy of the protein supply can be tested by comparing the nitrogen ingested with the nitrogen excreted—the nitrogen balance. This at once shows that proteins have a more complex metabolic history than carbohydrates or fats. In the first place, it is impossible in the healthy adult to induce a surplus of intake over output of nitrogen merely by feeding with excess of protein. There is no retention of nitrogen except during growth or convalescence. In the second place, reduction of nitrogen intake leads to an excess of output over intake, even though there may be an adequate carbon and therefore calorie supply. This adverse nitrogen balance is seen in its most extreme form in starvation, when the nitrogen output falls to a low value (about 10 gms.), which is constant day by day. When to the starving person is given daily an amount of protein corresponding to the amount of nitrogen which he lost daily when starvation was complete there is still an excess of output over intake. It is not until the nitrogen intake is two and a half times the starvation output that equilibrium is attained. But when in addition to the protein, carbohydrate or fat is given, nitrogen equilibrium is reached with a lower protein intake. This is the **protein-sparing** action of the non-nitrogenous foods.

These facts show that of the protein which is absorbed, part, in virtue of the carbon which it contains, goes to supplying energy—this is the part which can be replaced by carbohydrates or fats. The other part has a fate other than that of supplying energy—it becomes built up into the living cell.

From a study of the nitrogen balance we therefore come to the same conclusion regarding protein metabolism as we did from a study of the effect upon nitrogen elimination

of variations in the diet (p. 165). The fate of the protein is twofold : either exogenous or endogenous.

If the place of the exogenous portion of the protein absorbed can be taken by carbohydrate or fat it should be possible to reduce the protein intake very considerably—down to endogenous requirements, provided that non-nitrogenous food is given in abundance. This consideration led to the **Chittenden** experiments, in which different classes of people were fed on a very low protein diet for a period of several months. Chittenden claimed that health and working capacity were improved owing to diminished strain upon the kidneys and diminished intestinal putrefaction. If Chittenden's results are correct they constitute a severe indictment of human instinct, for man in almost every race takes a far more liberal protein supply. The experiments have been subjected to considerable criticism. The period over which they were performed, long as it was, was not long enough to allow conclusions to be drawn. Again, nations which for any reason subsist on a low protein diet are distinguished by a low degree of virility and increased susceptibility to bacterial infection.

The Need for Individual Amino-acids

A more serious criticism of Chittenden's theory is that for the purpose of maintaining the structure of the tissues it is the form of the protein that matters. The capacity of the animal body to manufacture amino-acids is, as we have seen, limited to very few of these. The majority have to be obtained from the food. Since the amino-acids are present in varying quantities in different proteins, and since in some proteins certain amino-acids may be present only in minute quantity, it follows that the adequacy of any given protein for tissue-building depends upon its content of the amino-acid present in least amount, and that any protein deficient in an amino-acid which the animal cannot synthesise is inadequate even though it may

have been given in liberal amount, measured by its nitrogen content. In other words, the *character* of the protein is of more importance than the *quantity*.

In the diet of civilised communities this question does not often arise owing to the fact that man has obeyed his instinct in taking a large and varied protein diet, thus ensuring that every amino-acid will be present in adequate amount. But when the protein intake is reduced, as in Chittenden's experiments, it becomes a question whether the border-line is not reached so far as any individual amino-acid is concerned.

Of recent years many experiments have been performed to demonstrate the need for individual amino-acids. The pioneer work was performed by Hopkins in 1906. Hopkins fed rats on a diet of protein, fat and carbohydrate, in which the protein took the form of zein—a protein deficient in tryptophane, lysine and glycine. Though the diet was abundant as regards its calorie value, the animals lost flesh and died within one to four weeks. On adding tryptophane to the diet, they lived some time longer and for a time maintained their weight. Later experiments have shown that on adding lysine as well as tryptophane growth and health are restored. Lysine and tryptophane, therefore, are needed by the living tissues.

Maintenance and Growth

Nutrition is adequate in the adult when it maintains the efficiency of the body, and in the young when in addition to this it provides for the normal rate of growth. What is the normal rate of growth? Growth depends upon two factors—the **growth factor** and the **food factor**. The growth factor is the inherent tendency to grow, which is subject to individual variations, depending upon the laws of heredity. It sets the upper limit to growth which no amount of feeding can overstep. The part which the food factor plays lies in providing the material upon which the growth factor can work. *The normal rate of growth*

is therefore the rate of growth determined and limited by the growth factor.

Is there a distinction between the food requirement for maintenance and the food requirement for growth? This question has been answered in the affirmative by Osborne and Mendel. These observers fed young rats on a diet in which the sole protein was *gliadin*, which is deficient in *lysine*, and found that they remained in good health but ceased to grow. On the addition of lysine to the diet the stunted animals resumed their growth. Lysine therefore, while not essential for maintenance, is necessary for growth, while its temporary absence from the diet does not lead to loss of the *capacity* to grow. Lysine is necessary for the full play of the growth factor.

ACCESSORY FOOD FACTORS—VITAMINES

Within the last few years there has been accumulating clinical and experimental evidence to show that something more is required in the diet than carbohydrates, fats, proteins and inorganic salts. There are also necessary certain substances which the animal cannot manufacture, and which must therefore be derived in the first instance from plants. They are termed *accessory food factors* or *vitamines*. For our knowledge of these substances we are indebted to Hopkins.

Their chemical nature is entirely unknown. As to the part they play in the animal economy, it is clear from the minute amounts which are sufficient that they do not contribute energy. They must therefore either form certain components of the cell architecture or play a part, like catalytic agents, in determining or regulating metabolic changes.

Absence of these substances leads in the young to failure of growth, and in both young and old to signs of malnutrition, decreased fertility, and abnormal proneness to infection, and in extreme cases to the development of certain specific diseases—"deficiency diseases."

There are three such food factors hitherto recognised :—

1. **Fat-soluble A.**—This substance is contained in most animal fats and oils. It is present also in the seeds and green leaves of plants, where its synthesis evidently occurs. Insoluble in water, it is soluble in anything which dissolves fats. It is destroyed by heating at 100° C. for four hours. Though not synthesised, it is evidently stored in the animal body, probably in the depot fat, for when the substance is withdrawn from the diet there is a slight delay before signs of malnutrition set in.

Present-day evidence suggests that deficiency of this substance is the primary cause of rickets.

2. **Water-soluble B.**—This substance is present in all foodstuffs in their natural condition. It is most abundant in yeast, in the embryo of seeds and in birds' eggs. It is soluble in water and alcohol, but not ether. It is resistant to drying and to heat at 100° C., but it is destroyed at higher temperatures. When it is absent from the diet pathological effects follow immediately, showing that it is not stored in the body. Recovery is equally rapid on its restoration. Deficiency of Water-soluble B causes a profound disturbance of the cerebral nervous system—muscular weakness and inco-ordination. Now a similar disturbance is found in the disease **beri-beri**, which occurs in communities where the sole diet consists of maize from which the embryo has been removed in the process of milling. An analogous condition produced in birds by similar feeding is called *avian polyneuritis*. It is believed by some that the "*anti-neuritic*" substance whose absence is responsible for beri-beri and polyneuritis is identical with Water-soluble B.

3. **Anti-scorbutic.**—This is the substance the absence of which causes scurvy. *It is present in tissues which are metabolically active*; it is absent from dry seeds, for instance, but appears on germination. It is readily destroyed by heat. It is present most abundantly in cabbage leaves, in lemons and in oranges.

What has been said above regarding nutrition may be thus summarised :—

1. Food is required for two purposes—maintenance and growth. There is some evidence that certain substances are necessary for the latter and not for the former.

2. The adequacy of a diet has a quantitative and a qualitative aspect. Quantitatively, an adequate supply of calories is required to provide energy for the life-processes. For this purpose proteins, fats and carbohydrates are to a great extent mutually replaceable. But besides the calorie supply there is need for certain substances which cannot be made by the animal body. Some of these are amino-acids. Others are bodies of unknown composition, called vitamins. These substances are necessary not as energy providers but as contributing some essential part of the cell-machine.

FAT SOLUBLE — D

— ANTI-RACHITIC

FAT SOLUBLE — E

— ANTI-STERILITY

water Soluble G

Pellagra Preventing

CHAPTER XII

URINE

Constitution of Urine

Total Quantity.—The average quantity passed by adults in twenty-four hours is 1500 c.c. Of this the greater part is secreted during the day.

Physical Characteristics.—Urine has a clear yellow colour, except after heavy meals, when it may be turbid, due to calcium phosphate and carbonate. On standing, these salts form a precipitate which redissolves on heating. The average specific gravity is 1018, but it varies between 1002 and 1040, according to the volume of urine passed.

Reaction.—Urine is normally acid to litmus. Its acidity is greatest after a meat diet, owing to formation of sulphuric and phosphoric acids. On a vegetable diet and during secretion of the acid gastric juice it becomes alkaline. The variability in the reaction of the urine is one of the means whereby the reaction of the blood is kept constant. When for any reason the PH of the blood decreases (*i. e.* the blood becomes more acid), the normal reaction is restored partly by excretion of acid sodium phosphate.

Urinary Pigments.

Urochrome.

Uroerythrine.

Urobilinogen—derived from bile pigment. On standing it is converted into urobilin.

Inorganic Constituents.

Metals.—Sodium, potassium and traces of Ca, Mg and Fe.

Acids.—Chlorides, phosphates and sulphates. Sulphur is also excreted in a less oxidised form of unknown constitution—*neutral* sulphur.

Average Constitution of a Daily Output of Urine

Total Quantity	1500	grms.
Water	1440	„
Total Solids	60	„
Urea	35.0	„
Uric Acid	0.75	„
Hippuric Acid	1.05	„
Ammonia	0.65	„
Creatinine	0.9	„
Sodium	5.5	„
Potassium	2.5	„
Calcium	0.26	„
Magnesium	0.21	„
Chloride	9.0	„
Sulphate	2.7	„
Phosphate	3.5	„

The history of the organic constituents is discussed under metabolism.

Functions of the Kidney

The functions of the kidney are three:—

1. To remove waste products from the blood;
2. To keep the volume and saline content of the blood constant;
3. To keep the reaction of the blood constant.

In considering the manner in which urine is formed it must be remembered that although we use the word *secretion* in this connection, the kidney differs from a secreting gland, such as a gastric gland, in the following fundamental respects.

1. Developmentally it is of mesodermal origin, while most other glands are formed by invagination from the gut.

2. With the exception of hippuric acid, the kidney does not elaborate the substances which it secretes. It merely separates them from the blood and alters their concentration.

3. The kidney being an excretory organ, its activity is readily influenced by changes in the composition of the blood with which it is supplied.

To account for the manner in which the kidney performs its work it is necessary to explain—

1. Why some substances are separated from the blood while others are not;

2. How the former came to attain a different degree of concentration in the urine from that in which they exist in the blood;

3. What part is played in the process by the glomerulus and what part by the tubules;

4. Whether the process can be explained on physical grounds or whether it is necessary to invoke the specific activity of the cells;

5. How diuretics act.

THE FORMATION OF URINE

Structure of the Kidney

Certain essential features of the renal anatomy must be borne in mind. The functional unit of the kidney consists of glomerulus, Bowman's capsule and the tubule. The **capsule** is the dilated blind end of the tubule invaginated to form a cup. In this cup is situated the **glomerulus** or tuft of capillaries. The invaginated layer of the capsule is formed of thin, flattened epithelium, which embraces the glomerulus. The tubule follows a devious route towards the pelvis of the kidney. In its first part, the **first convoluted tubule**, it is, as its name implies, much twisted. Here it lies entirely in the cortex. This leads into the second part, the **descending limb**, which pursues a radial course into the medulla. Arrived there, it doubles back upon itself at the **loop of Henle**, and returns to

the cortex as the **ascending limb**. This leads into the **second convoluted tubule**, beyond which it unites with neighbouring tubules to form one of the **junctional tubules** which traverse the medulla radially and open at the apex of a pyramidal projection into the pelvis of the kidney.

The cells lining the tubule differ in different parts. In the first and second convoluted tubules and in the upper half of the descending limb the cells are high columnar, with well-marked striations formed of rows of granules in the outer half and at the inner free border, which is ciliated. Though the tube is wide the lumen is small. In the rest of the tubule, the lumen is wider and the cells lining it are flattened.

Blood Supply.—In the surface of separation between cortex and medulla, the renal vessels form an arcade. The artery gives off branches which traverse the cortex radially. From these branches arise lateral twigs which lead into the glomeruli. The venules draining these break up to form a network surrounding the tubules. From this network the blood is conveyed to the renal veins.

The blood supplying the kidney, therefore, like that supplying the viscera, passes through a double system of capillaries. It is now established that the tubules receive no direct arterial supply.

Nerve Supply.—The *renal plexus* situated at the hilum of the kidney receives fibres (1) from the sympathetic, emerging from the lower thoracic segments of the cord, and (2) from the vagus.

The *action of the sympathetic* is to cause diminution of secretion by vaso-constriction. Though this nerve is said to contain vaso-dilator fibres, its constrictor influence is paramount.

The function of the vagus is unknown.

The kidney appears to be supplied with no secretory fibres. Although it is liberally supplied with nerves, these are not essential to its activity. The kidney when excised and immediately replaced soon resumes its functions.

Theories of Renal Function

The first conception of the renal mechanism emanated from Bowman in 1842. Based on anatomical considerations, it was an attempt to differentiate the functions of the glomeruli from those of the tubules. Bowman suggested that the glomeruli secreted a saline solution which in passing down the tubules dissolved and separated urea and uric acid from the cells of the tubules. The whole process was a physical one.

Two years later this view was combated by Ludwig, who believed that from the glomeruli appeared a solution which consisted of plasma minus the proteins. The function of the tubules was to concentrate this fluid. Ludwig was at first emphatic in declaring both processes to be purely physical, but later, discovering that the constituents of the urine differed quantitatively from those of the blood, he withdrew from this position and was ready to admit some power of selection on the part of the cells.

In 1874 Bowman's theory, which had been more or less eclipsed by Ludwig's, was revived in a modified form by Heidenhain.

Heidenhain, like Bowman, located the secretion of the water and salts in the glomeruli, and that of the other solids in the tubules. He differed from Bowman in very definitely attributing both processes to the selective power of the urinary cells.

It will be seen that the controversy is a double one. First, is the separation of urine from the blood due to passive filtration or to active secretion? Secondly, is the function of the tubules to secrete urinary constituents or to absorb water? The one point on which there is universal agreement is that the urine becomes in some way concentrated as it passes down the tubules. But it must be emphasised that the differentiation of the glomerular from the tubular function is based entirely on the histological appearance of these structures. *As long as we are ignorant of the nature of the glomerular fluid, concentration in the tubules must remain an assumption.*

THE MECHANISM OF URINE FORMATION

If the separation of fluid in the kidney is due to filtration, the process must obey the following three laws:—

1. The amount of filtration will vary directly with the blood-pressure in the glomeruli and inversely with the pressure in the tubules.

2. The tendency to filtration will be resisted by the osmotic pressure of those constituents of the blood which do not pass through the glomeruli; filtration ceasing when the filtration pressure is counterbalanced by such osmotic pressure.

3. Any variation in the amount of urine filtered will not be accompanied by variation in the oxygen consumption of the kidney.

Let us now see whether these conditions hold.

1. *The Filtration-pressure.*—As regards the pressure in the glomeruli the results are set forth in the accompanying table.

Experiment.	General blood pressure.	Renal vessels.	Kidney volume.	Urinary flow.
Division of spinal cord in neck	Falls to 40 mm.	Relaxed	Shrinks	Ceases
Stimulation of cord	Rises	Constricted	Shrinks	Diminished
Stimulation of cord after section of renal nerves	Rises	Passively dilated	Swells	Increased
Stimulation of renal nerves	Unaffected	Constricted	Shrinks	Diminished
Stimulation of splanchnic nerves	Rises	Constricted	Shrinks	Diminished
Plethora	Rises	Dilated	Swells	Increased
Hæmorrhage	Falls	Constricted	Shrinks	Diminished

Here it will be seen that the amount of secretion is influenced not by the general blood-pressure but by the degree of dilatation of the renal arterioles—that is to say, by the local blood-pressure in the kidney.

When the pressure in the ureter is raised by partially clamping this vessel the rate of flow falls. This might, however, be due not to the reduction in the filtration pressure but to the obstruction of the veins consequent upon the dilatation of the tubules.

2. *The Osmotic Pressure of the Plasma Colloids.*—The proteins of the plasma exert an osmotic pressure of 25–30 mm. of mercury. When the arterial blood-pressure is reduced to 40 mm. the flow of urine ceases. Allowing for a certain difference between the arterial pressure and the pressure in the renal arterioles, these facts indicate that the cessation of flow occurs because the filtration pressure is neutralised by the osmotic pressure. In confirmation of this explanation is the fact that when the ureter is obstructed the pressure rises within it until it is about 30–40 mm. below arterial pressure.

The protein content of the plasma may be reduced by partially replacing the blood by a suspension of corpuscles in Ringer's solution. When this is done there occurs a copious diuresis which cannot be explained by the change in the viscosity of the blood. Clearly the proteins by their osmotic pressure restrain the tendency to filtration.

3. *The Consumption of Oxygen.*—This question has been settled by Barcroft and Straub, who studied the gaseous metabolism of the kidney upon the injection of salts. The result is shown in Fig. 29, from which it will be seen that when Ringer's solution is injected there is a diuresis unaccompanied by increased oxygen consumption. Under these circumstances the energy is derived not from the kidney but from the heart.

There is therefore convincing evidence that physical factors play a very important part in the formation of urine.

Function of the Tubules

In spite of innumerable experiments made with a view of deciding whether the tubules secrete substances in solution or absorb water, the question cannot be said to have been decided. The chief reasons for this are that in many experiments conditions are so unreliable that no conclusion can be drawn from them, while in other

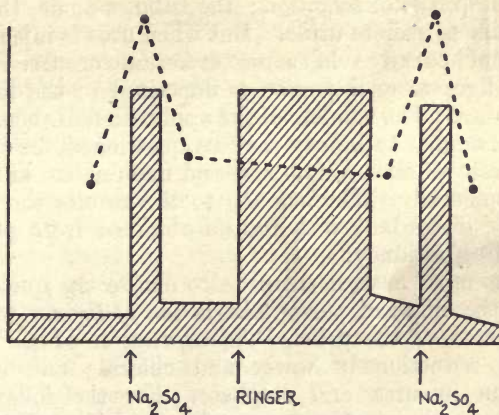


FIG. 29.—Diuresis and oxygen consumption (after Barcroft and Straub). Dotted line = oxygen consumption; shaded area = amount of urine secreted.

experiments the results are equally well or equally badly explained on either theory.

1. Heidenhain decided the point to his own satisfaction by injecting substances into the circulation and afterwards examining their deposition in the kidney. Using **Sodium Sulphindigotate**, he showed that shortly after injection the stain appeared in the cells of the tubules, while later on it appeared in the lumen of the tubules. For long these experiments were regarded as proof of tubular secretion, but they are now known to be fallacious. The

fact appears to be that at present we have no histological method of distinguishing between two opposite processes.

2. *Nussbaum's Experiment.*—Nussbaum sought light on the subject from the frog's kidney. In the amphibian, it will be remembered, the renal artery supplies first the glomerulus, then the tubule, as in the mammal, but the tubule receives, in addition, blood conveyed from the limbs by the renal portal vein. Ligature of the renal artery causes stoppage of secretion; the tubules alone, therefore, are unable to secrete urine. But when urea is injected into the renal portal vein some secretion occurs. Sodium sulphindigotate on injection is deposited in the lumen of the tubules. The validity of the application of these results to the mammalian kidney may be questioned, for although structurally similar, amphibian and mammalian kidney are developmentally different. As to the results themselves, they are discordant with results obtained from perfusion of the frog's kidney.

3. Attempts have been made to decide the question by noting the effect of *partial obstruction of the ureter* on the composition of the urine. This operation causes a well-marked reduction in water and chloride and a slight reduction in urea and sulphate. For the followers of Heidenhain this means decreased secretion at the glomeruli. For the followers of Ludwig it means increased absorption.

Experiments in which the tubules have been removed by gouging out the medulla may be dismissed as causing too much injury to the kidneys. Similarly attempts to poison the tubules by injection of mercuric chloride are open to the objection that the permeability of the glomeruli is altered by this procedure.

It is clear that the formation of urine can only be accounted for by filtration when its composition is that of plasma minus proteins. This is the case in the diuresis caused by injection of Ringer's solution. When the composition of the urine differs from this the process must be

due to the physiological activity of the tubules, whether this takes the form of absorption or secretion.

In Fig. 29 it is shown that when sodium sulphate is the cause of diuresis the oxygen intake is greatly increased—evidence of work being done by the cells. In diuresis thus caused the concentration of the dissolved substances in the urine differs materially from their concentration in the plasma.

Cushny's Theory

The most remarkable feature in the action of the kidney is that the character of the secretion is influenced by the composition of the blood. When from any cause the latter is disturbed the kidney reacts in such a way as to restore it to the normal. The urine is usually more concentrated than the blood; but it may be more dilute, as when large quantities of water have been drunk.

It follows, therefore, that no theory of renal function is complete unless it takes into account the adaptive nature of the mechanism. This point of view is uppermost in the most modern theory of renal secretion—that due to **Cushny**. Cushny accepts filtration as sufficient to account for glomerular activity. He believes the glomerular fluid to consist of plasma minus proteins. He regards the function of the tubules as one of active absorption of water *and of substances in solution, the composition of the reabsorbed fluid being practically Ringer's solution, whatever may be the composition of the blood or the urine.*

Cushny has arrived at this conclusion by a comparative study of the concentration of the principal constituents in blood and in urine. Some of the blood constituents, *e.g.* dextrose, sodium and chlorides, only pass into the urine when they have attained a certain concentration in the blood. These he calls **Threshold Bodies**. Others, *e.g.* urea and sulphates, appear in the urine when present only in traces in the blood. These he calls **No-Threshold Bodies**. In between these groups are **Intermediate Bodies**

such as uric acid and potassium, which have a Threshold, but the Threshold, unlike that of the Threshold Bodies proper, is habitually exceeded under normal conditions. All these substances, to whichever category they belong, pass through the glomerulus, but they differ greatly in the degree to which they are reabsorbed.

No-Threshold Bodies like urea are not absorbed at all. Threshold Bodies like dextrose are reabsorbed provided that they do not exceed the threshold in the blood. When the threshold is exceeded, the excess fails to be absorbed and appears in the urine.

Cushny's example will make this clearer.

	67 litres plasma contain		62 litres filtrate contain	61 litres reabsorbed fluid contain		1 litre urine contains	
	%	Total		%	Total	%	Total
Water . .	92	26 l.	62 l.		61 l.	95	950 c.c.
Colloids . .	8	5360 gms.	—				
Dextrose . .	0.1	67 gms.	67 gms.	0.11	67 gms.		
Uric Acid . .	0.002	1.3 „	1.3 „	0.0013	0.8 „	0.05	0.5 gms.
Sodium . .	0.3	200 „	200 „	0.32	196 „	0.35	3.5 „
Potassium . .	0.02	13.3 „	13.3 „	0.019	11.8 „	0.15	1.5 „
Chloride . .	0.37	248 „	248 „	0.40	242 „	0.6	6.0 „
Urea . .	0.03	20 „	20 „			20	20 „
Sulphate . .	0.003	1.8 „	1.8 „			0.18	1.8 „

One litre of urine contains 2 per cent. of urea. The blood contains .03 per cent. Therefore the litre of urine is formed from $\frac{2}{.03} = 67$ litres of plasma. The plasma contains 62 litres of water. Therefore 62 litres pass through the glomerulus. Of this amount 61 litres are reabsorbed. The

colloids, which amount to 8 per cent. of the plasma, are retained in the blood.

The dextrose, which amounts to 0.1 per cent., filters through the glomerulus, but, being within its threshold, it all passes back through the tubules. Were it to exceed the threshold, as in diabetes, the excess would pass into the urine, while the previous amount would continue to be reabsorbed. The same applies to sodium and chloride. As regards the uric acid, Cushny reminds us that this (in mammals, at any rate) is not an end product of metabolism in the same sense as urea, but that there is always an attempt on the part of the body to convert uric acid into urea. Uric acid therefore possesses a low threshold. It is incompletely excreted, but any excess in the blood affects the urine, not the reabsorbed fluid. Potassium behaves in a similar manner. As for urea and sulphate, their fate is simple. They are never reabsorbed.

It will thus be seen that however the composition of the blood may vary, the substances which pass through the glomeruli are always returned to the blood in amounts up to their threshold values, while excess passes over to the urine. *The composition of the reabsorbed fluid is constant.* If, for example, the blood is more dilute, a more dilute glomerular filtrate is formed. But the composition of the reabsorbed fluid being unaltered, the result is that the dilution only affects the urine.

An objection which might at first sight be urged against this theory is the large amount of reabsorption of water which is entailed, one litre of urine corresponding to 67 litres of plasma. But when it is remembered that the daily flow of blood through each kidney is estimated at 900 litres, this objection falls to the ground.

DIURETICS

These may be divided into two groups:—

1. Substances usually present in blood.
2. Foreign substances.

1. The first group act as diuretics by being present in blood in excess. According to Cushny they cause diuresis in two ways.

(a) By **Dilution diuresis**. By this is meant the diuresis brought about by dilution of the colloid content, and therefore by diminution of the osmotic pressure of the blood. Among the substances which act in this manner are *water* and the Threshold Bodies such as *chlorides*.

(b) By **Osmosis**. While all saline substances cause a certain degree of dilution diuresis, some, and in particular the No-Threshold Bodies such as *sulphates*, act also by exerting through their osmotic pressure a restraining influence on the process of reabsorption of water.

2. *Foreign Substances*.—The principal members of this class are caffeine, digitalis and pituitary extract. Their main diuretic action is probably an indirect one through their effect upon the circulation. Whether they also stimulate the renal cells is undecided.

THE EXCRETION OF URINE—MICTURITION

The passage of urine down the ureters is due partly to gravity, partly to pressure of fluid from the tubules, partly to waves of contraction. The ureters pass through the bladder wall obliquely—by this arrangement the pressure inside the bladder prevents the return of urine into the ureters.

The orifice of the bladder is guarded by three sphincters. Of these, one, the most proximal, is the *sphincter trigoni*, situated at the neck of the bladder. This is essentially an involuntary muscle, though there may be some volitional control over it. The other two sphincters, the *compressor urethrae* and the *bulbo-cavernosus*, are voluntary.

Nerve Supply.—The bladder is innervated (1) by sympathetic fibres emerging from the 11th and 12th dorsal and 1st and 2nd lumbar segments and reaching it by the inferior mesenteric ganglion and hypogastric nerves,

(2) by sacral automatic fibres from the 2nd and 3rd sacral segments. These travel by the pelvic nerves and terminate by arborising around ganglia situated in the bladder wall. From these ganglia fibres pass to the muscles.

Stimulation of the sympathetic causes inhibition of the body of the bladder and contraction of the sphincter; that of the sacral autonomic, inhibition of the sphincter and contraction of the body. Both nerves contain afferent fibres.

The factors contributing to the act of micturition will be best understood if we consider (1) the action of the isolated bladder; (2) the action of the bladder when in connection with the lumbo-sacral part of the cord; (3) the modification of (2) due to connection with the higher centres. First, however, it is necessary to understand the relation between the degree of distension of the bladder and the pressure within the organ.

As the bladder fills, *the pressure within it at first remains practically unaltered*, the wall simply giving before the gradual accumulation. When distension has reached a certain point, further filling causes a rise of pressure—the wall is now in a condition of increased tonus. At this stage slow **rhythmic contractions** make their appearance. These become more vigorous until eventually one occurs which is sufficient to overcome the tonic contraction of the sphincter. This mechanism occurs in the isolated as well as in the normal bladder.

Normally micturition occurs when the pressure is about 160 mm. of water. The degree to which distension occurs before the pressure begins to rise depends upon the rate at which the bladder fills. When this is rapid, rise of pressure occurs early, so that only a small amount of urine is voided. The same effect is also produced when the bladder wall is unduly irritable.

In the bladder separated from the cord the forcing open of the sphincter due to the rhythmic contraction of the bladder wall results in an evacuation which comes to an

end as soon as the intravesical pressure falls below that which is required to keep the sphincter open. *The bladder is therefore never completely emptied*—a fact of great clinical importance.

When the connections between the bladder and cord are intact but the cord transected in the thoracic region, stretching of the bladder wall not only causes rhythmic contraction but gives rise to impulses which travel to the cord when they reflexly produce impulses motor to the body of the bladder and inhibitory to the sphincter. By this means the bladder is emptied completely, and the urethra is emptied by reflex contraction of the muscles surrounding it. Purely reflex micturition of this sort can be brought about by stimulation of any sensory nerve, particularly those arising in the pelvis.

In the intact organism the mechanism is to a great extent under the control of the will. The sudden rise in intravesical pressure is recognised subjectively. The evacuation of the bladder is aided by contraction of the abdominal muscles. There is evidence, too, that the sphincter trigoni and even the musculature of the bladder wall are under voluntary control.

CHAPTER XIII

INTERNAL SECRETION

INTERNAL secretion is the elaboration by an organ of a specific substance, which passes into the blood-stream and exerts a stimulating or inhibiting effect upon some function of the body. In some cases the formation of an internal secretion is not the sole function of the organ. The ovary and testes, for instance, in addition to forming the morphological elements of reproduction, pour into the blood substances upon the presence of which depend the development of secondary sexual characteristics. The duodenal epithelium, besides secreting the gastric juice externally, secretes secretin internally. The pancreas not only forms the pancreatic juice, but also secretes into the blood, probably from the Islets of Langerhans, a substance which regulates carbohydrate metabolism.

In some organs the formation of an internal secretion constitutes their only function. Of these there are three of outstanding importance—the thyroid and parathyroid apparatus, the suprarenal glands, and the pituitary body. It is with these that we are mainly concerned in the present chapter.

The substances secreted are known as **hormones**. They are not enzymes, for they are of much simpler constitution; they are dialysable and are not destroyed by heat. Some have been isolated, and one—adrenalin—can be prepared synthetically.

Methods of Investigation of the Organs of Internal Secretion

Our knowledge of these organs has been derived—

1. From their structure, development and comparative anatomy;

2. From the effects of extirpation;

3. From the effects of *administration* of the glands intravenously and orally both to normal animals and to those from which the gland has been extirpated; from the action of the extract upon isolated organs and from the effects of transplantation;

4. From pathological conditions associated with changes in these organs;

5. From a comparative analysis of the blood entering, and the blood leaving, the organ.

THE THYROID AND PARATHYROID GLANDS

Structure and Development of the Thyroid

The thyroid consists of closed vesicles bounded by a single layer of epithelium. There being no basement-membrane, the vesicles are separated from one another solely by areolar tissue, in which lie the profuse blood-vessels, lymphatics and nerve-filaments, the last-named being derived from the superior and inferior laryngeal branches of the vagus, and from the sympathetic. The cavity of the vesicles is usually distended with a *colloid* substance. In some animals the appearance of the vesicles can be modified by changing the diet. When rats are fed with lean meat the epithelium is cortical or even flattened, and the vesicles loaded with colloid. When the diet consists of bread and milk the epithelium is columnar, and shows evidence of active secretion; at the same time the lumen, diminished in size by the protrusion of the cells, contains a serous fluid but little or no colloid. The colloid thus appears to represent a store of secretion, which exists when the gland is relatively inactive (Figs. 31 and 32).

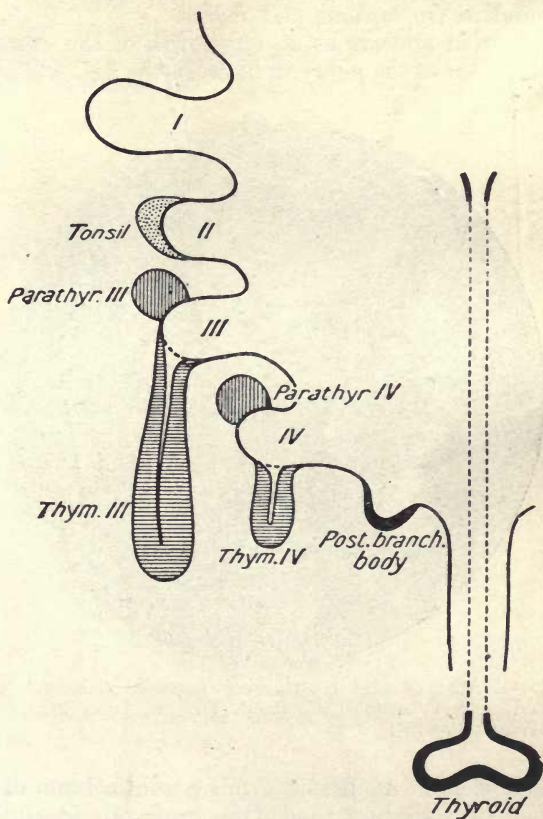


FIG. 30.—Origin of thyroid, parathyroids and thymus in the mammalian embryo. I, II, III, IV, branchial pouches. The post-branchial body in mammals either disappears or becomes incorporated with the thyroid (from Schafer, *The Endocrine Organs*).

What is believed to be the active principle of the thyroid has now been isolated, and is known as **thyroxin**. It is a compound of *tryptophane* and *iodine*.

The thyroid appears as an outgrowth of the entoderm, lining the floor of the pharynx between the first and second

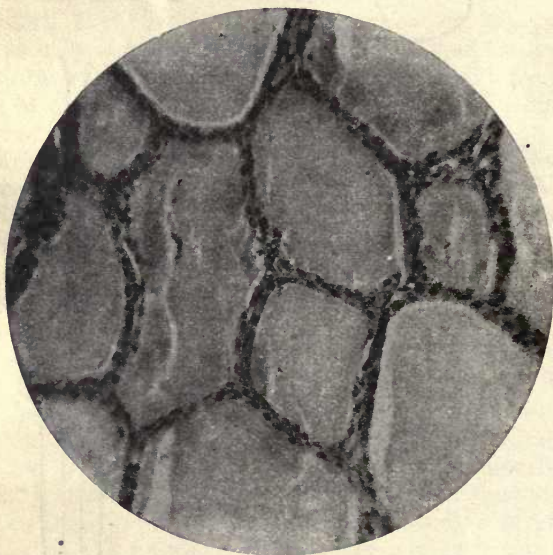


FIG. 31.—Thyroid of wild rat showing flattened cells and vesicles distended with colloid (Chalmers Watson, from Schafer, *The Endocrine Organs*).

branchial clefts. At first it forms a solid column of cells which, opposite the upper end of the trachea, divides into two lateral parts. From these, by a process of budding, the thyroid is formed. The solid column becomes temporarily canalised and serves as a duct. After this it disappears, its pharyngeal extremity persisting as the foramen cæcum of the tongue (Fig. 30).

Structure and Development of the Parathyroid

The four parathyroids, which are either attached to the thyroid or embedded in it, are composed of epithelial cells arranged sometimes compactly together, sometimes in lobules which are separated by connective-tissue

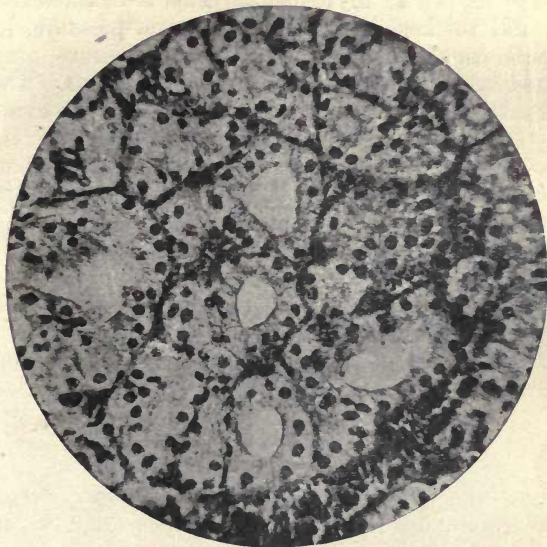


FIG. 32.—Thyroid of another wild rat showing columnar cells and absence of colloid (Chalmers Watson, from Schafer, *The Endocrine Organs*).

liberally endowed with blood-vessels. The cells are mostly small, and may be either clear or granular. A colloid substance is sometimes seen lying between them. This is said to increase in amount after removal of the thyroid. The parathyroids receive the same nerves as the thyroid.

The upper and lower pairs of parathyroids are developed

from the 3rd and 4th branchial clefts respectively (see Fig. 30).

Thyroid Deficiency

In the adult, degeneration of the thyroid causes the condition known as **myxœdema**. This is characterised by a dry and thickened skin which pits on pressure, loss of hair, subnormal temperature, low blood-pressure, muscular weakness and hypotonus, and mental dullness. There is a general diminution of the metabolic processes evidenced by a lessened oxygen intake and nitrogen excretion. There is an increase in sugar tolerance and a tendency to deposit fat. Regeneration of tissue after injury is impaired.

In children, to the above signs are added failure of growth and of mental and sexual development. This is the condition known as **cretinism**.

In short, deficiency of the thyroid leads to a slowing down of all the bodily functions.

In animals analogous changes can be induced by removal of the thyroid, the parathyroids being left intact.

Excess of Thyroid

The activity of the thyroid is increased during pregnancy and lactation, during puberty and menstruation, in the sexual act and other emotional states.

Exophthalmic goitre is a pathological enlargement of the thyroid associated with increased activity. It is characterised by a rapid pulse, high blood-pressure, muscular tremors, protrusion of the eyeballs, and an excitable, nervous state. There is a general quickening of the metabolic processes and a loss of body fat. Sugar-tolerance is diminished. Histologically the gland shows evidence of active secretion—irregularity of the vesicle walls indicating an increase of surface from which secretion can occur—the columnar form of cell and absence of colloid.

Administration of Thyroid Extract

In the normal individual this causes slight lowering of blood-pressure, tachycardia, restlessness, flushing of the skin, sweating, increased nitrogen excretion and diminution of body fat. Sugar tolerance is decreased.

In the cretinous or myxœdematous individual it causes a rapid cure of the physical and mental condition.

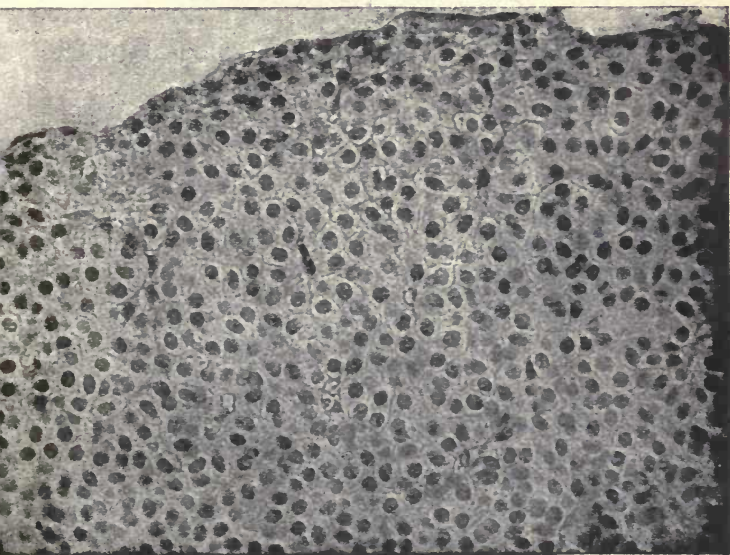


FIG. 33.—Parathyroid of cat (Schafer, *The Endocrine Organs*).

Parathyroid Deficiency

Removal of all the parathyroids with the thyroid usually causes the condition known as **tetania parathyropriva**. The muscular system undergoes fibrillar twitchings which develop into well-marked clonic contractions, and culminate in convulsive seizures. Vomiting, diarrhoea and

wasting lead to death in a few days. If but one parathyroid is left behind this condition does not occur.

It has been observed among Himalayan children that in certain cretins nervous manifestations are prominent. In these the parathyroids have been found to be specially involved.

Recently considerable evidence has accumulated to show that parathyroid deficiency is associated with disturbance of **guanidine**¹ metabolism. The evidence is as follows :—

1. Guanidine is formed in the intestine by bacterial putrefaction.

2. During intestinal putrefaction, symptoms resembling tetania parathyropriva make their appearance. In this condition the guanidine content of the blood and urine is increased.

3. Guanidine increases in the blood after removal of the parathyroids.

4. Tetany can be induced by injection of guanidine.

As regards the effect of administration of parathyroid extracts we have no reliable information.

The evidence above detailed seems to show that thyroid and parathyroids subserve functions which are entirely distinct. The thyroid, while not essential to life, is necessary for the proper speeding up of all the bodily functions. To quote McCarrison, "the thyroid gland is to the human body what the draught is to the fire." The parathyroids elaborate a substance which neutralises a toxin, probably guanidine, which acts upon the neuromuscular system.

THE SUPRARENAL GLANDS

Structure

Each suprarenal gland consists of two parts, the cortex and the medulla. The cortex is composed of epithelial

¹ See page 177.

cells, and is differentiated into three layers, by the way in which these cells are arranged. From without inwards these layers are—

1. *Zona glomerulosa*, in which the cells have an alveolar formation.

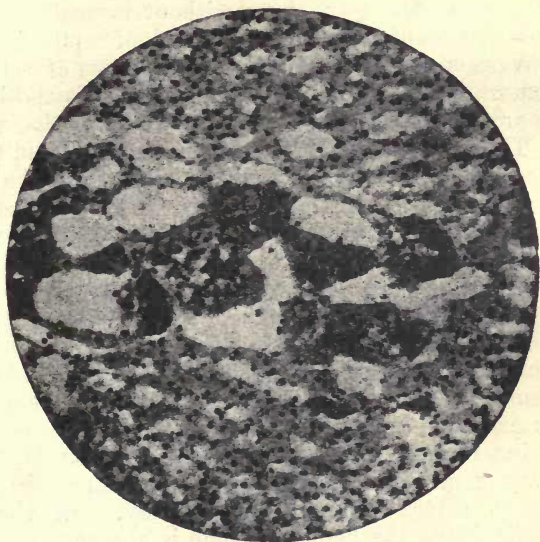


FIG. 34.—Suprarenal cells of medulla stained brown with potassium bichromates. Note the blood sinuses continuous with those of the zona reticularis (Schafer, *The Endocrine Organs*).

2. *Zona fasciculata*, where they form single columns, running radially.

3. *Zona reticularis*, in which they form an open mesh-work.

The cortical cells contain a doubly refracting lipid composed of lecithin and cholesterol esters. In the innermost layer they contain a pigment.

The medulla consists of a mass of cells permeated by blood-sinuses. The cells are irregular in shape and contain granules, some of which stain brown with chromates. On this account they are called **Chromaffin cells**.

Of all organs in the body, the suprarenals receive, for their weight, the most abundant blood supply. The blood passes through the gland from without inwards. In the two outer layers of the cortex a network of capillaries runs in the connective tissue, between the columns of cells but not penetrating them. In the zona reticularis the blood-vessels are dilated and occupy the spaces between individual cells. They run into the blood-sinuses of the medulla.

There is a liberal nerve supply, derived from the sympathetic, filaments passing in through the cortex and forming a plexus, containing ganglion cells, among the cells of the medulla.

Development and Morphology

The cortex is of mesodermal origin, being formed from the Wolffian ridge in conjunction with the primitive kidney and genital gland. The human foetus is peculiar in that the cortex is abnormally large, owing to great development of the inner layer or "boundary zone." After birth the boundary zone degenerates, and at the same time the permanent cortex develops superficially. In the an-encephalic foetus the boundary zone is absent.

The medulla is of epiblastic origin. At an early stage of development certain nerve cells migrate out of the spinal cord. Some of these form the sympathetic ganglia; others become enclosed by the cortex of the suprarenal, and form the medulla. The former, of course, are in connection with peripheral structures through their post-ganglionic fibres, and with the cord through the pre-ganglionic fibres. The medullary cells retain their connection with the cord, but assume a secretory function.

The cells of the medulla therefore correspond to sympathetic ganglion cells.

In the fish cortex and medulla remain separate; in amphibians they adjoin; in mammals the cortex encloses the medulla.

Functions of the Suprarenal Glands

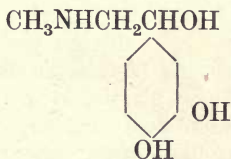
Notwithstanding that the blood-supply in the mammal suggests that cortex and medulla function together, the wide difference in the origin of the two parts, and the fact that they remain distinct in many animals, indicate that the functions of the cortex and medulla are separate.

The Cortex

We have no definite information regarding the function of the cortex. Two suggestions may be mentioned. The first, based on the high content of lipoids, is that it is concerned with the *manufacture of lipoids* to be used elsewhere. The second is that the cortex plays a part in connection with the development and activity of the sexual organs. Enlargement of the cortex occurs during pregnancy; hypertrophy in children is constantly associated with sexual precocity.

The Medulla—Adrenalin

From the chromaffin cells is secreted *adrenalin*, which has the formula—



Adrenalin is remarkably active physiologically. It acts upon every organ endowed with sympathetic fibres in a manner identical with stimulation of these fibres. Its most striking effect is upon the blood-vessels, especially

those of the splanchnic system, in which it induces powerful vaso-constriction. In the intact animal the heart may be slowed—a reflex effect due to the increased blood-pressure, but after section of the vagi the beat is much accelerated and augmented. The pupils are dilated and the eyeballs protruded. The salivary glands are either paralysed or secrete a scanty thick saliva. The intestines are relaxed, but the ileo-cæcal sphincter and the sphincter ani are contracted. The body of the bladder is relaxed and the neck of the bladder constricted. In the male the retractor penis is stimulated; in the female the uterus is sometimes stimulated, sometimes inhibited. The bronchioles are relaxed. The sweat glands are stimulated and the hairs erected.

The liver is stimulated to increased sugar production, sugar appearing in the urine. It is also said that the recovery of fatigued muscle is accelerated and that coagulation of the blood is hastened.

The action of adrenalin is not upon the sympathetic nerve endings, for the drug is still effective after degeneration of the nerves. Nor is its action upon the peripheral organ itself, since it has no effect upon structures which have no sympathetic supply. It is therefore believed to act upon a *receptor substance* (neuromuscular junction) lying between the nerve-ending and the organ.

An increase in the adrenalin content of the suprarenal veins has been shown to occur on experimental stimulation of the splanchnic nerves and during violent emotions.

Disease of the Suprarenals (Addison's disease).—Usually due to tuberculosis of the glands, it is characterised by low blood-pressure, feeble heart action, abdominal pain, vomiting, extreme muscular weakness, and pigmentation of the skin. It is invariably fatal.

The circulatory disturbance is referable to deficiency of adrenalin in the circulation.

Removal of both glands causes muscular weakness, lowering of blood-pressure and cardiac failure, death

occurring usually within forty-eight hours. When the animal is moribund, stimulation of vaso-constrictor fibres is without effect upon the blood-vessels.

Administration of suprarenal extract, whether to patients suffering from Addison's disease or to animals from which the glands have been removed, at most only prolongs life slightly.

It is clear that the function of the medulla is to produce adrenalin. The part which adrenalin plays in the animal economy, like the part which the sympathetic nerves play, is to adapt the animal to efforts of defence or offence in emergency. The quickened heart-beat, the varied blood-pressure, the intestinal paralysis, the relaxation of the branchioles, the secretion of sweat, the mobilisation of sugar, are all means to this end.

THE PITUITARY BODY

Structure

The pituitary body is composed of three parts, which are histologically distinct.

The *Pars Anterior* consists of a mass of epithelial cells, some of which contain basophile granules, some oxyphile granules. In others the protoplasm is clear. These cells abut on large blood-sinuses. The pars anterior is incompletely separated by a narrow cleft from the

Pars Intermedia.—Although continuous with the pars anterior at the circumference of the cleft, the pars intermedia differs in certain respects from the pars anterior. It is less vascular; the cells contain neutrophile granules, and are here and there disposed in vesicles which contain colloid. The pars intermedia is closely adherent to the

Pars Posterior (or Nervosa).—This consists of neuroglial fibres and cells and has only a scanty blood supply. Appearances have been described which suggest that the colloid material secreted by the pars intermedia passes into the

pars nervosa, up into the infundibulum, and enters the third ventricle. Other observers deny this.

The pituitary receives nerve fibres from the cervical sympathetic.

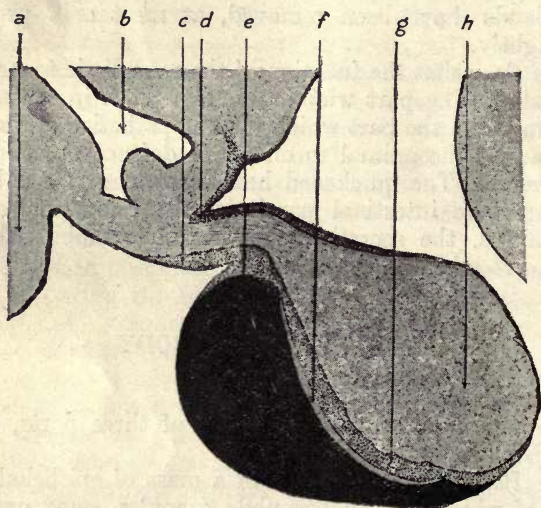


FIG. 35.—Mesial sagittal section through the pituitary body of an adult monkey (semi-diagrammatic): *a*, optic chiasma; *b*, 3rd ventricle (infundibulum); *e*, pars anterior; *f*, cleft; *g*, pars intermedia; *h*, pars nervosa (Herring).

Development

The anterior and intermediate parts are derived from an outgrowth of the buccal epithelium (*Rathke's pouch*), the cleft between them being the remains of the original lumen of the invagination. The pars nervosa develops as a hollow downgrowth of the third ventricle. In man the cavity becomes obliterated.

It will therefore be seen that the pars intermedia, while *morphologically* related to the pars anterior, becomes

associated anatomically with the pars nervosa. *Pars intermedia* and *pars nervosa* together constitute what is commonly known as the posterior lobe.



FIG. 36.—Pituitary of cat: *a*, pars anterior; *b*, cleft; *c*, pars intermedia; *d*, pars nervosa (Schafer, *The Endocrine Organs*).

Functions of the Pituitary

Pituitary Extract.—An extract of the posterior lobe (pars intermedia and pars nervosa) has the following effects:—

The heart (with vagi cut) is slowed, but individual beats are augmented. Blood-pressure is increased by vasoconstriction, but the effect is not repeated on a second dose.

All plain muscle is contracted, the most striking effect being upon the uterus.

The renal cells are stimulated—causing diuresis.

A secretion of milk occurs, due, however, not to activity of the glands but to squeezing out of the milk already present by contraction of the muscle fibres.

The assimilation limit of sugar is lowered.

Extract of the pars nervosa is more effective in producing the above effects than extract of the pars intermedia.

Extract of the pars anterior is inactive.

Disorders of the Pituitary.—Two conditions are associated with affections of the pituitary—**acromegaly** and **dystrophia adiposo-genitalis**.

In acromegaly there is an enlargement of the face, hands and feet, due chiefly to great hypertrophy of the bones. There is abnormal muscular development, thickening of the skin, overgrowth of hair, and sometimes diminished carbohydrate tolerance. This condition is attributed by Cushing to superactivity of the pituitary. If the disturbance sets in before ossification is completed, all the long bones undergo a great increase in length—**pituitary gigantism**.

Dystrophia adiposo-genitalis is believed to be due to insufficiency of the pituitary, the signs being the reverse of those found in acromegaly. Growth and sexual development are defective. The mind is lethargic and the temperature subnormal. There is marked adiposity and an increased sugar tolerance, 200–300 grms. of glucose being absorbed without glycosuria occurring.

In this condition administration of an extract of the anterior lobe relieves only the subnormal temperature, while extract of the posterior lobe only raises the low blood-pressure and lowers the sugar-tolerance.

Removal of the Pituitary.—It is now agreed that complete removal of the pituitary is rapidly fatal, the terminal event being ushered in with lethargy, general weakness, tremors, cardiac weakness, subnormal temperature, and coma.

Removal of the pars nervosa alone causes no symptoms. Removal of a large portion of the anterior lobe is incompatible with life, but when a small portion only is removed there develops a condition resembling dystrophia adiposogenitalis—atrophy of the genital organs and deposition of fat. The same condition can be produced experimentally when the pituitary is deprived of its blood supply by section of the infundibular stalk. When this is done the cells of the anterior lobe undergo atrophic changes.

The functions of the pituitary, so far as we know them, may be thus summarised :—

The anterior lobe is essential for life; the posterior lobe is not only not essential but its absence causes no symptoms.

The anterior lobe seems to have a profound influence upon bodily, and particularly skeletal, growth.

The biological significance of the physiological effect of posterior lobe extract is not known.

THE PINEAL GLAND

This is a small body situated in the root of the third ventricle. Morphologically it is related to the median eye of the reptile. It is composed of epithelial cells with profuse blood-sinuses. Proportionally larger in youth, it afterwards undergoes atrophy.

Little is known of its function. Abnormal growth and sexual precocity have been variously associated with excision, with disease, and with injection of pineal extract.

GENERAL FEATURES OF THE ORGANS OF INTERNAL SECRETION

It is of interest to note that the three organs which we have discussed at length—the thyroid and parathyroids, the suprarenals, and the pituitary—have the following features in common :—

1. Each is composed of two parts, which are distinct in their development and structure, and appear to be distinct in their functions. Whether such duality is of biological significance, or is mere fortuitous, we cannot say.

2. The organs in the course of development undergo a curious transformation in disposition, and sometimes in their very nature. The medulla of the suprarenal originates as a mass of migrating nerve cells; the anterior lobe of the pituitary is formed from a gland opening to the mouth.

3. Their blood supply is remarkably profuse, indicating a high degree of activity.

4. In all cases complete extirpation causes death.

5. Extract of one component is more active physiologically than extract of the other.

Interaction of the Internal Secretions

A feature of the internal secretions is that they all influence, in one direction or the other, certain fundamental biological processes, such as carbohydrate metabolism, growth, and sexual development. As regards carbohydrate metabolism, sugar tolerance is diminished by injury to the pancreas, by injection of adrenalin and by over-activity of the thyroid or pituitary. It is increased by deficiency of the thyroid or pituitary. Growth is influenced by the thyroid, pituitary and the suprarenal cortex. Abnormal sexuality is associated with hypertrophy of the cortex of the suprarenal; arrested sexuality is found in cretinism and subpituitarism.

Furthermore, the glands are not without influence upon

one another. Removal of the thyroid causes hypertrophy of the pituitary; disease of the pituitary leads to overgrowth of the thyroid. The regulation of the metabolic processes therefore depends upon a balance between the activities of all the internal secretions. The disturbance which follows the absence of one secretion may be due, not directly to such absence, but to the unchecked activity of the secretions which remain.

CHAPTER XIV

THE REGULATION OF TEMPERATURE

THE energy liberated by the metabolic processes appears as physiological activity and as heat. Of these the former is a primary, the latter a secondary or incidental effect. In cold-blooded animals the heat evolved is immediately lost by conduction and radiation to the environment. The temperature of these animals is therefore only slightly higher than that of the surrounding medium. But heat, while it is the result and not the cause of metabolic changes, has a considerable influence upon the rate at which such changes occur; the rate of metabolism varying in cold-blooded animals directly with the external temperature. This is seen in the rise in CO_2 output which in the frog accompanies rise of temperature. In warm-blooded animals there is developed a mechanism for the conservation of the heat produced by cell activity, in such a manner that the temperature of the body is maintained at an almost uniform level which is independent of and higher than the usual temperature of the environment. Owing to the rapidity of the circulation all the internal organs are practically at the same temperature.

The advantages of this arrangement are obvious. The constancy of the temperature abolishes any dependence of functional activity upon the environment, while its tropical level is suitable for the rapidity of metabolic changes.

In man the body temperature, as usually taken, in the mouth or axilla, is 36.9°C . (98.4°F .). A more accurate

record of the temperature of the internal organs is obtained from the rectum or from the urine. Normally there is a daily fluctuation between 37.5°C . (99.5°F .) in the evening and 36.2°C . (97.2°F .) in the early morning. This is due to the greater bodily activity which occurs during the daytime, for it is reversed in those who follow nocturnal employment.

The constancy of the temperature is due to a balance between the heat produced and the heat lost.

Heat is produced solely in the metabolic processes, principally in the voluntary muscles.

Heat is lost—

- (1) By radiation to the surrounding atmosphere;
- (2) By evaporation of sweat;
- (3) By evaporation of water in the lungs;
- (4) By discharge of warm excreta—carbonic acid, urine and fæces;
- (5) By warming foods ingested cold.

Heat regulation is seen in its simplest form in muscular exercise when increase in heat-production is counter-balanced by an increase in heat-loss brought about by dilatation of the cutaneous blood-vessels and increased evaporation of sweat from the skin and of water from the lungs.

Variations in the external temperature produce a two-fold reaction—change in the amount of heat lost (physical regulation) and change in the amount of heat produced (chemical regulation). These alterations being in a reciprocal direction the temperature remains constant.

Physical Regulation

The action of external cold upon the skin is to constrict the blood-vessels and to stop sweating. These effects are produced reflexly through the central nervous system, the sensory nerves constituting the afferent and the sympathetic the efferent path. In the absence of

such a mechanism the heat lost would, of course, increase as the external temperature fell. Now physical regulation only partially compensates for this, for the heat lost still rises with fall of temperature, but not to the same extent as would occur were the mechanism absent. Physical regulation therefore produces a relative, not an absolute diminution in heat-loss. The amount of heat lost is further diminished by the instinctive act of putting on more clothes, these serving as a means of entangling a layer of warm air around the body. Radiation of heat is less in the obese than in the thin, the heat of the body being preserved in the former by the subcutaneous fat.

Chemical Regulation

The increased heat-production is again a reflex effect. To its occurrence, which can be demonstrated by calorimetry, several factors contribute:—

- (a) Increased inclination to voluntary activity;
- (b) Involuntary movements—shivering;
- (c) Increased tonus of the muscles.

In dogs, when the passage of impulses from brain to muscles is blocked by administration of curare, the animal loses the power of maintaining a constant temperature when the temperature of the environment falls.

Increased metabolism leads to increased appetite. Food is taken in larger quantity, and when absorbed adds the heat due to its *specific dynamic energy* (p. 153). Observations on the respiratory quotient show that this approaches unity—proving that the increase in metabolism chiefly involves the carbohydrates.

As the surrounding temperature rises, heat-loss increases owing to the discarding of clothes, the diminished vaso-constriction and, later, the secretion of sweat. At the same time, heat-production is decreased owing to a progressive disinclination for activity and a diminished

muscular tone. Heat-production, however, cannot be diminished below the *basal metabolism* which, we have seen, amounts to about 2500 C. When this limit is reached the temperature can only be maintained at a constant level by increased loss of heat—that is by radiation and evaporation.

Radiation is facilitated by the constant removal of the warmed air from the surface of the body; it is therefore more effective in a wind than in a still atmosphere. As the surrounding temperature rises, conduction diminishes and evaporation comes more and more into play, until when the temperature of the air is as high as or higher than that of the body evaporation becomes the sole avenue for heat-loss. The effectiveness of evaporation depends upon the degree of saturation of the air with water-vapour. When the air is so hot that radiation cannot occur, and so humid that evaporation cannot occur, the heat-regulating mechanism breaks down and the body temperature rises.

A centre for the regulation of temperature is said to exist in the *corpus striatum*. Damage to this area leads to rise of temperature. Stimulation with water colder than the blood leads to shivering and vaso-constriction, stimulation with water warmer than blood to diminished muscular tone and to vaso-dilatation. The rise of temperature which occurs during fevers (pyrexia) is attributed to the stimulation of the centre by the toxic products of the infective process.

CHAPTER XV

THE NERVOUS SYSTEM

PART I

THE NEURONE AND THE NERVOUS IMPULSE

THE functions of the nervous system are to co-ordinate the activities of the different organs of the body and to bring the body into relation with its environment.

The cells of which the nervous system are composed are distinguished by possessing in an exalted degree two properties, *irritability* or the capacity to respond to a stimulus, and *conductivity* or the capacity to transmit a disturbance arising at any point in the cell with great rapidity throughout the whole cell. Out of these two properties arise others—the capacity to store impressions and to associate them together—properties upon which depend the more complex mental processes.

THE NEURONE

The nervous system is made up of a chain of nerve-cells or neurones, each of which consists of a cell-body and one or more processes. These processes are of two kinds, *axons* and *dendrons* (or *dendrites*). The cell-body is the enlarged part of the neurone which contains the nucleus. It is the meeting-place of the processes if more than one exist, and if only one process exists it is the part at which the neurone comes into anatomical contact with the

processes of neighbouring neurones. The cell-body is sometimes known as the nerve-cell. It should be remembered, however, that the whole neurone, processes and all, is one cell. The cell-body contains a well-marked nucleus, within which is a nucleolus. In a perfectly fresh cell the protoplasm surrounding the nucleus contains fine granules uniformly distributed. Shortly after death these granules clump together and form the *Nissl bodies*, which stain readily with methylene blue. But although entirely a post-mortem phenomenon, the formation of Nissl bodies fails to occur (*chromatolysis*) unless the cell was previously in a healthy state. It fails when the cell has undergone prolonged disuse or excessive fatigue.

Among the granules, and traversing the cell-body from dendrites to axon are fine fibrils which join together to form a plexus.

According to the number of processes arising from the cell-body the nerve-cell is known as *unipolar*, *bipolar*, or *multipolar*. However many processes the cell may possess, only one is termed an *axon*. Collections of cell-bodies outside the central nervous system are known as ganglia, and inside are often termed nuclei.

Nerve-fibres

These are the processes of the nerve-cells. They are of two kinds: white or medullated, and grey or non-medullated. Medullated fibres consist typically of three layers. The innermost layer—the *axis cylinder*—is composed of fine longitudinal fibrils continuous with those of the cell-body. Surrounding the axis cylinder is the *medullary sheath*, composed of a lipoid substance known as myelin. It is non-nucleated and probably structureless. It is interrupted at intervals—the *nodes of Ranvier*. The medullary sheath probably serves to protect, nourish and insulate the axis cylinder.

Surrounding the medullary sheath is the *neurolemma* or *sheath of Schwann*. This forms a thin nucleated and un-

interrupted investment. At the nodes, when the medullary sheath is deficient, it is contiguous with the axis cylinder. The neurolemma is only found in nerve-fibres outside the central nervous system.

The above description applies equally to dendrons and to axons. These differ in that dendrons branch very freely, while axons, though they give off minute lateral branches (*axon collaterals*), do not properly divide until near their termination.

Under physiological conditions an impulse travels from the dendrons to the cell-body and from the cell-body to the axon (axipetal conduction).

Non-medullated fibres, as their name implies, have no medullary sheath. Upon them lie nuclei believed to belong to a kind of neurolemma. They ramify more freely than medullated fibres.

In the nerve-trunk the nerve-fibres are packed together in bundles, which are separated by connective tissue—the perineurium. This contains blood-vessels, lymphatics and sensory nerve-endings (*nervi nervorum*). Surrounding it is an outer fibrous layer—the epineurium.

Degeneration and Regeneration of Nerve

When a nerve is cut, the axons which are separated from their cell-bodies undergo the process of **Wallerian degeneration**. The medullary sheath is decomposed into a mass of fatty globules, and the axis cylinder becomes broken into fragments. The *débris* is absorbed by leucocytes. Meanwhile the nuclei of the sheath of Schwann undergo proliferation, forming a chain of cells in which fibres are deposited. Regeneration—a slow process—occurs by down-growth of fibres from the central stump. These find their way into the peripheral part, the newly formed fibres of which form a kind of scaffolding for the new nerve processes to grow down.

When a motor nerve is cut profound changes take place in the muscle which it supplies. There is a high degree

of atrophy and depression of excitability. The muscle ceases to respond to the alternating current. At make and break of the constant current it responds with a sluggish contraction. Further, while a normal muscle responds better to a closing (make) current when stimulated by the kathode than when stimulated by the anode ($KCC > ACC$), in the degenerated muscle it responds to kathode and anode indifferently.

THE NERVOUS IMPULSE

We shall now consider the excitability and conductivity of the nerve-fibre with a view to understanding the nature of a nervous impulse.

Velocity

The rate at which a nervous impulse travels is estimated in the nerve-muscle preparation by stimulating the nerve first at one point, then at another point along its course, and measuring the difference in the latent period. For the frog the velocity is twenty-eight metres per second. For warm-blooded animals it is probably at least five times as great, the rate of conduction increasing considerably with rise of temperature.

Reversibility of the Impulse

A disturbance arising at any point in a nerve-fibre is transmitted throughout the fibre in both directions. This was proved by the classical experiment of Kühne. The frog's gracilis muscle consists of two halves, separated by a fibrous band; each axon as it enters the muscle divides, one branch going to each half of the muscle. Stimulation of one half of the muscle where it contains nerve-endings causes contraction of the whole muscle, the impulse having travelled up one set of branches of the axon to the point of division and down the other set.

An analogous phenomenon is found in connection with

the bladder. The innervation of this viscus is shown in Fig. 37. After section of the nerves going to the inferior mesenteric ganglion, when the left hypogastric nerve is cut and its central end stimulated, the right half of the bladder contracts. This is due, as Langley and Anderson showed, to the division of each axon going to the inferior

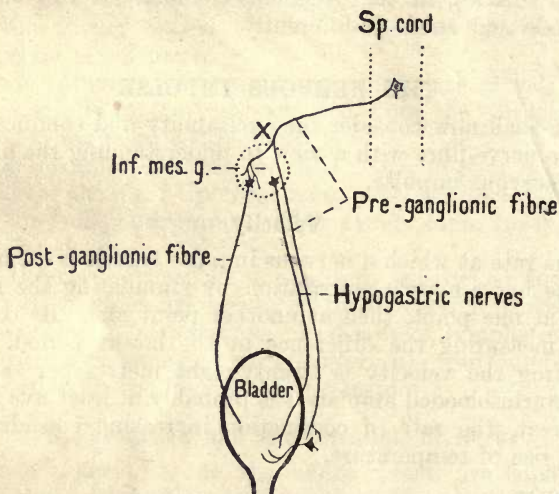


FIG. 37.—Diagram to show the axon-reflex in the innervation of the bladder. The axons divide at x (from the *Journal of Physiology*).

mesenteric ganglia. Such an effect is termed an **Axon-reflex**.

The question now arises, if nerve-fibres can conduct impulses in both directions, do they do so under natural conditions? It is usual to regard nerve-fibres as either exclusively motor or exclusively sensory, but the antidromic impulses (p. 87) seem to indicate that the posterior root-fibres, in addition to conveying sensory impulses centrally, convey vaso-dilator impulses peripherally. Again,

when the posterior root ganglion is diseased, an eruption occurs along the cutaneous distribution of the nerve (herpes zoster).

The Excitability of the Nerve Fibre

The nerve-fibre, like any other part of the neurone, is highly irritable; it responds to various stimuli, such as heat, or the action of chemicals by an internal disturbance which is propagated throughout the neurone and culminates in a subjective impression or a motor effect. Of all the stimuli or exciting agents the most convenient to employ for experimental purposes is electricity, for although this is a form of energy which but rarely affects nerves under normal conditions, yet it is the only one which in this connection can be measured.

When a constant current is passed through a nerve, excitation occurs at make and again at break. While the current is passing no visible result is produced. In nerve, as in muscle, the state of excitation begins at the kathode on make and at the anode on break. Change of potential, then, rather than potential itself, is the stimulating agent.

On inquiring further into the effect of change of potential upon the development of the excitatory state, it is found that there are two separate factors concerned—the *intensity* of the current and the *rate of change* of potential. As to the latter there is for nerve as for every irritable tissue an optimum rate of change or gradient which is effective. This is known as the “*characteristic*.” The high-frequency current, for instance, is harmless to the body, since the rate of change is too rapid to influence any of the tissues. The single induction shock, while an efficient stimulus to nerve, is too rapid for less irritable tissues, such as intestinal muscle.

Yet though no excitation occurs while the constant current is passing, duration of current is an important factor. There is between duration and intensity of current a reciprocal relation; the smaller the current, the longer

must it last in order to be effective. The following figures by Keith Lucas show this :—

Duration of current in seconds.	Strength of current in volts.
∞	·086
·00087	·179

Here the smallest current which is effective, given unlimited time, is ·086 volt. When the strength of current is doubled the minimum duration required is ·00087 sec. This figure was called by Lucas *the excitation-time*. He found it to be smaller in nerve-fibre than in muscle, and much smaller, again, in the nerve-ending.

Factors influencing the Activity of the Nerve-fibre

The two properties possessed by the nerve-fibre—excitability or the capacity to initiate a disturbance, and conductivity or the capacity to propagate that disturbance—are both profoundly modified by various circumstances.

1. *Temperature*.—The rate of conduction increases considerably with rise of temperature. The change in excitability depends upon the form of current used. With rise of temperature nerve becomes more irritable to induction shocks and less irritable to mechanical stimulation.

2. *Previous Activity*.—Provided that the nerve-fibre is liberally supplied with oxygen it seems to be completely immune to fatigue. When, after the motor nerve-endings have been paralysed with curare, a nerve is subjected to prolonged stimulation the muscle which it supplies contracts when the effect of the drug has passed away.

But the effect of a stimulus is influenced by an impulse which has just occurred, the direction in which it is influenced depending upon the interval between the stimulus and the previous impulse. The most notable change is a change in excitability. This is shown in Fig. 38. For a period of about ·002 sec. after an impulse has passed along it a nerve is completely inexcitable. This

is known as the **absolute refractory period**. Then follows the **relative refractory period**, during which the excitability is steadily rising to the normal. This is succeeded by a period of heightened excitability, the **supernormal phase**. It will be noted that the refractory period of nerve differs from that of muscle in being much shorter.

It is now known that these three phases in the change

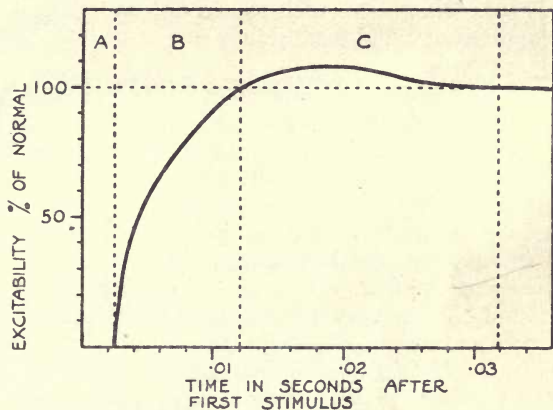


FIG. 38.—Diagram (after Adrian and Lucas) to show recovery of excitability after the passage of an impulse: A, absolute refractory period; B, relative refractory period; C, supernormal phase.

in excitability are accompanied by corresponding changes in conductivity.

It follows as a corollary from this that if a nerve is stimulated while it is in the supernormal phase due to a previous stimulus, the initiation and propagation of the second impulse will be facilitated—the disturbance will be greater and will travel more rapidly than it would had there been no previous stimulus. If two stimuli, each of which acting alone would be ineffective, are sent into a nerve such that the second enters while the nerve is in

the stage of exalted excitability due to the first, the second stimulus becomes effective. This is known as **summation**.

3. *The Passage of a Constant Current—Electrotonus.*—Though there is no propagated disturbance while a constant current is passing through a nerve there is a change in excitability, known as *electrotonus*. This takes the form of diminished excitability at the anode (*anelectrotonus*) and increased excitability at the kathode (*katelectrotonus*).

4. *Drugs.*—Narcotics, such as alcohol and CO_2 , depress both conductivity and excitability.

The Changes accompanying a Nervous Impulse

1. *Current of Action.*—When an impulse passes along a nerve-fibre this shows a current of action resembling that found in muscle, the part of the nerve which is in a state of excitation being negative to the rest of the nerve. On this is based a method for determining whether a nerve is active *in situ*, *e. g.* the depressor nerve.

2. *Evolution of Heat.*—By means of the thermopile it has been found that a very minute though indisputable rise of temperature accompanies the passage of an impulse.

3. *Gaseous Metabolism.*—When a nerve-fibre is deprived of oxygen it loses its excitability more rapidly when it is stimulated than when it is not. This shows not only that oxygen is necessary for the maintenance of the fibre in a healthy condition, but also that oxygen is used up in the passage of a nervous impulse.

Similarly it has been shown that the CO_2 output of a nerve is increased 2.5 times when it is stimulated. These facts therefore point to an unmistakable gaseous interchange accompanying a nervous impulse.

The Nature of the Nervous Impulse

From the fact that a nervous impulse is generated on make of a constant current at the kathode, and on break at the anode, and that it depends upon the rate of change of current rather than upon the current itself, the

hypothesis has been put forward that the initiation of an impulse depends upon the rate of change of concentration of ions at the point stimulated. More certain is our knowledge concerning the nature of the impulse when it is being propagated. There are two possibilities. Either the impulse is launched with a certain quantity of energy which carries it to its destination, or it is dependent for its conduction upon a renewal of energy by molecular changes at each successive point in its course. In the first case we should expect to find that a nerve-fibre is capable of carrying impulses of different strength according to the intensity of the energy with which the impulse is started. In the second case the intensity of the disturbance would be independent of the strength of stimulus and dependent only upon the nerve-fibre itself. The fibre, in other words, would obey the **all-or-none principle**. Proof that the latter supposition is true comes from Adrian's experiment. When a given length of nerve is narcotised for a certain time the impulse is extinguished as it traverses the narcotised portion. Suppose that a length of nerve D (Fig. 39, A) is narcotised in such a way that the impulse started at III is just abolished at the distal end of D. Now suppose this length to be divided into two, d and d' , separated by a length of healthy nerve I. When the impulse emerges from d it will be reduced to half its intensity. If it remains at this intensity until it enters d' it will again be completely extinguished at the distal end of d' . Its intensity will be represented as shown by the continuous line in Fig. 39, B. If, on the other hand, the impulse arrives at the muscle with undiminished force, it means that every time it enters a healthy part of the nerve it recovers its initial intensity as shown in Fig. 39, C. Adrian found the latter to be the case, thus proving that the nervous impulse rather resembles a train of gunpowder. If a part of the train is slightly damp there is a delay in the rate of conduction, but provided that the molecular changes are able to pass through the

damp part the conduction in the dry part beyond is in no way impaired. This experiment shows that the impulse depends for its conduction upon energy liberated along its course, and that the nervous impulse obeys the all-or-none law in that its intensity is independent of the intensity of the stimulus to which it owes its origin.

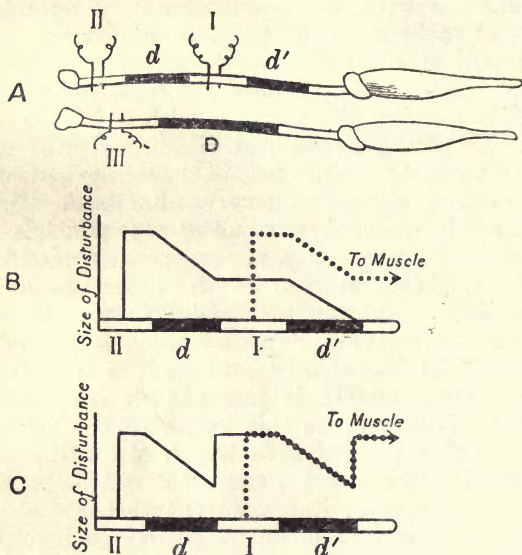


FIG. 39.—Adrian's experiment (from the *Journal of Physiology*).

In confirmation of this view is the evidence, already given, of a definite increase in the metabolism of a nerve-fibre when it is active.

Conduction from Nerve to Muscle

The axis cylinder pierces the sarcolemma of the muscle-fibre and arborises in a mass of protoplasm known as the

end-plate. The latter therefore forms an anatomical break in the neuro-muscular mechanism. This break has a definite physiological significance, for it possesses certain special properties on account of which the nature of the impulse passing along it differs from an impulse passing along a nerve-fibre. (1) There is evidence to show that the end-plate is more liable to fatigue than the nerve-trunk; (2) there is a delay in the transmission of the impulse across it; (3) impulses traverse it in one direction only—from nerve to muscle; (4) it responds to stimuli of extremely short duration; (5) it is peculiarly susceptible to the action of drugs.

It is therefore believed that between the nerve-ending and the muscle-fibre a third substance exists differing physiologically both from nerve and from muscle. This substance forms a structure called the **neuro-muscular junction**.

PART II

THE CENTRAL NERVOUS SYSTEM

By means of the nervous system an animal reacts to changes in its environment. The physical form which the reaction takes is the expression of the ability of the animal to overcome the alteration in the external circumstances; the reaction is purposive and protective. Evolution from lower to higher forms is distinguished by nothing so much as by an increase in the variety both in degree and in kind of the responses which the organism is able to make.

The earliest formation of cells specialised to respond to stimuli is seen in *Hydra* (Fig. 40, I), where certain epithelial cells are endowed with a high degree of irritability on their superficial surface and with a high degree of contractility on their deep surface—this being expanded to form a contractile plate. The next stage is the migration of the contractile element away from the epithelium so that it may be exposed to the environment. Accompanying this migration is a separation of the single responsive cell into two, one specially endowed with irritability, the other with an exalted contractility (Fig. 40, II). The connection between the two cells is by a strand of the irritable cell—the first appearance of a nerve-fibre. In a third stage this strand acquires a nucleus of its own and becomes an independent cell (Fig. 40, III). We now have a contractile cell responding to a stimulus arising in another cell situated at a distance from it. The fourth stage consists in the establishment of a means of co-ordination between

all the neuro-muscular mechanisms in the organism. This is effected by free anastomosis of the nerve-fibres—an arrangement of which the best instance is seen in the jelly-fish (Fig. 41). Here a plexus of nerve-cells and nerve-fibres connects all the sensory cells on the outer surface with all the contractile cells in the interior, the nerve-fibres being continuous throughout. This has been termed the **diffuse** nervous system. Such an arrangement has its advantage and its limitation. The advantage is that the whole motor apparatus can be immediately brought into action as the result of a stimulus arising at any one spot on

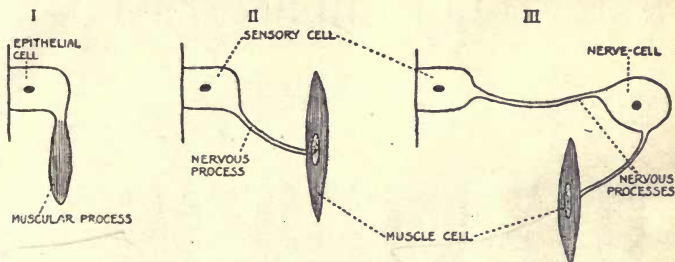


FIG. 40.—Diagram (after Foster) to show the evolution of the nervous system.

the epithelium. The limitation is that the whole muscular mechanism must be brought into play if at all. Owing to the freedom of the nervous connections no contraction of parts of the muscle sheet is possible. But from the nature of the organism this is not necessary, since locomotion, which is the only response possible, can only be brought about by a contraction of the whole swimming-bell. The response, then, in this stage is always crude and maximal. It is possible that the nerve-net system is represented in Auerbach's plexus of the intestine.

The development of the capacity for graded responses is the fifth and last stage in the evolution of the nervous system. It is associated with the appearance of the

central or **synaptic** nervous system. Out of the single continuum of nervous tissue is evolved a system of nerve-cells or neurones which form a complex chain, adjacent links of which are functionally continuous, but, so far as is known, histologically discontinuous, the gaps which separate the neurones being known as *synapses*. As an impulse traverses a synapse it is liable, as we shall see, to modification both in intensity and in character. It is

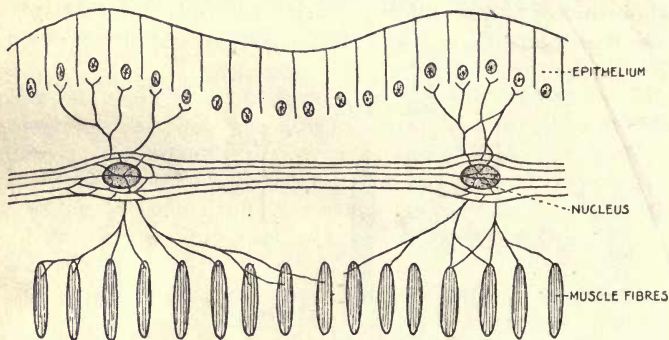


FIG. 41.—Diagram of part of body-wall of Medusa (jelly-fish), after Bethe.

owing to the special physiological characters of the synapses that the animal is enabled to grade and to alter in kind the form of its nervous response.

Synapses or junctions between neurones are collected together into groups, and in segmented organisms each segment has its own synaptic centre, the centres of all the segments being connected together by nervous strands. In this way is formed the beginning of a spinal cord which serves the purpose of conducting an impulse from one segment to another, and thus of co-ordinating the activities of all the segments for the good of the whole organism.

The animal, being now elongated along one axis, develops at one end (the front end) epiblastic cells specialised to receive stimuli from a distance—light, smell and, later, sound-waves. In this way it is enabled to explore new territory before moving into it. The information gained from these sensory cells largely determines the reaction of the organism, the rest of the body becoming subservient to the advancing end. With the greater responsibility thrown upon this region, the neurones belonging to it undergo considerable increase in number and complexity—in this way the cerebrum is formed.

But in addition to knowledge of the external world, the animal requires information regarding its own position. In different parts of the body special cells are developed to be excited by position and by change of position. These impulses converge upon masses of nerve-cells lying behind the cerebrum and forming the cerebellum.

THE TRACTS OF THE CENTRAL NERVOUS SYSTEM

The following methods have been employed for tracing the course of fibres *within* the central nervous system:—

1. **Fleschig's Myelination Method.**—This depends upon the fact that in different tracts the axis cylinders acquire their myelin sheaths at different stages of embryonic development.

2. **Wallerian Degeneration.**—The histological changes which follow the separation of a nerve-fibre from its cell-body have already been noted. In about three weeks after section, the myelin is converted into a simple fat which can be stained with osmic acid (Marchi's method).

3. **Successive Degeneration.**—This is a modification of the above method. Fig. 42 represents a longitudinal section of the cord, A, B, C and D being the segments. It is desired to find out what descending neurones arise in the segment B. The cord is transected between A and B and several months allowed to elapse, so that all fibres arising

from above B (1, 2 and 3) undergo complete degeneration and disappear. Section is then made between B and C, and three weeks later the newly-degenerated fibres (4, 5 and 6) arising from B will be visible lower down on staining with osmic acid.

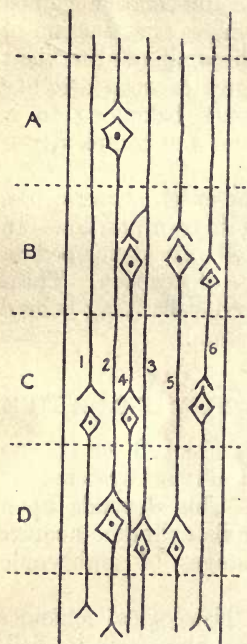


FIG. 42.—To show the method of successive degeneration.

4. Retrograde Degeneration.—When a nerve-fibre is cut, though the proximal part does not undergo Wallerian degeneration, the cell-body undergoes a diminution in size and chromatolysis or failure of formation of the Nissl bodies—changes which can be readily made out by staining with methylene blue. In this way it is possible, for example, to find out from what cells in the cord a motor nerve arises.

5. Histological Method.—The tissue is stained in bulk with methylene blue or silver nitrate.

The main tracts are the following:—

Descending Tracts :—

1. Pyramidal Tracts.— These arise from large cells (Betz cells) situated in the *motor or pre-Rolandic area* of the cerebral cortex. As they pass inwards they form a converging mass of fibres—*corona radiata*.

They then form in turn the posterior limb of the *internal capsule* and the middle part of the *crus cerebri*. In the pons some of the fibres end by arborising around the *nuclei pontis*, the fibres of which pass transversely to the cerebellum in the middle peduncle. These transverse fibres break up the main tract into a number of bundles,

which, however, are collected together again in the medulla, where they form the ventrally placed *pyramids*. At the lower end of the medulla the great majority of the fibres cross over (*decussation of the pyramids*) and occupy an area in the lateral columns of the cord (**crossed pyramidal tract**) (Fig. 43, 1). They terminate at different levels by passing into the grey matter and arborising around cells in the anterior horn and at the roots of the posterior horn.

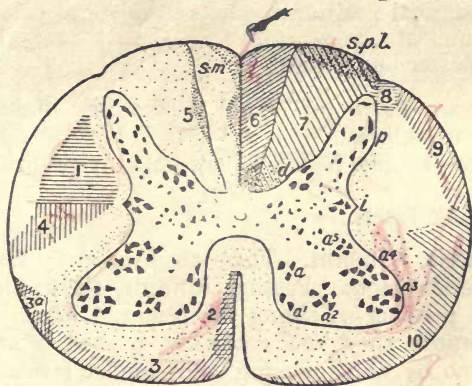


FIG. 43.—Diagram showing the ascending (right side) and the descending (left side) tracts in the spinal cord (from Schafer's *Essentials of Histology*).

A few fibres (*uncrossed lateral pyramidal tract*) pass into the lateral columns of the same side.

Some fibres (*direct pyramidal tract*) pass into the anterior columns of the cord on the same side (2).

2. Prepyramidal or Rubrospinal Tract (*Bundle of Monakow*).—This bundle arises in the *red nucleus* of the mid-brain, through which it gains connection with the cerebellum. In the cord the fibres occupy a position anterior to the pyramidal tract (4) and end in the grey matter, joining the anterior and posterior horns.

3. Tecto-spinal and Olivo-spinal Tracts (*Bundle of*

Helweg).—These tracts arise from the *anterior* and *posterior corpora quadrigemina* and from the *olive*. Passing downwards they cross over and occupy in the cord a small area opposite the outermost point of the anterior horn (3, *a*).

4. **Vestibulo-spinal or Anterolateral Descending Tract.**—Arising in *Deiters' nucleus*, through which it gains connection with the cerebellum, this tract occupies in the cord a marginal position in the anterolateral column (3).

Short Descending Tracts :—

5. *Comma Tract* (5).—The descending branches of posterior root-fibres.

6. *Septo-marginal bundle* (5, *m*).—Mainly proprio-spinal.

Ascending Tracts :—

1. **Posterior Columns.**—These are formed by fibres from the posterior roots. Passing inwards, these fibres first occupy a position adjoining the posterior horn. As they pass upwards they are gradually pushed towards the middle line by fibres coming in at higher levels. In the upper part of the cord the posterior column becomes divided into two parts—a *postero-median part* (**Column of Goll**), containing fibres from the lower limb, and a *postero-lateral part* (**Column of Burdach**), containing fibres from the upper limb. These fibres terminate at different levels by entering the grey matter, the largest travelling into the medulla, where the column of Goll arborises around the **nucleus gracilis**, and the column of Burdach around the **nucleus cuneatus**. From these nuclei a second relay of fibres takes origin, and decussating in the medulla, forms the **median fillet**, which ends in the **optic thalamus**. From the thalamus a third neurone travels to the cerebral cortex.

The fibres of the posterior column are uncrossed in the cord.

2. Cerebellar Tracts :—

The Direct or Dorso-lateral Cerebellar Tract (*Tract of Flechsig*) arises from the cells of **Clarke's column** (situated internally on the posterior horn), occupies a dorsolateral position in the cord and enters the cerebellum by the *inferior peduncle*, ending in the lower part of the vermis. This tract is uncrossed.

The Indirect or Anterolateral Cerebellar Tract (*Tract of Gowers*).—These fibres arise from Clarke's Column, form a ventrolateral tract and enter the cerebellum by the superior peduncle, ending in the superior part of the vermis. They are mainly uncrossed.

3. Spino-thalamic and Spino-tectal Tracts.—Intermingled with the Tract of Gowers are a few fibres travelling upwards to the thalamus and corpora quadrigemina. They are partly crossed, partly uncrossed.

PART III

REFLEX ACTION

WITH the exception of the axon-reflexes, already described, all reactions to stimuli in the higher animals occur through the central nervous system. Such reactions are called reflex actions. In order to study them it is necessary to transect the spinal cord in its upper part in order to eliminate influences due to cerebral processes, such as willed movements. An animal so prepared is known as the spinal animal. For our knowledge of reflex action we are indebted to the researches of Sherrington.

Examples of Reflex Action :—

1. *The Flexion Reflex.*—When the skin of the foot in the spinal animal is pricked, burnt or stimulated electrically the foot is drawn up.

2. *The Extensor Thrust.*—When pressure is applied to the pad of the foot the leg is fully extended.

3. *The Scratch Reflex.*—When any point over a wide area of the back and flank is stimulated the hind leg performs a rhythmic scratching movement directed to the point stimulated.

In reflex paths three component parts can be made out :—

1. A **receptor** organ, situated peripherally. This structure is endowed not only with a high degree of irritability, but also with the power of responding to stimuli of a particular kind.

2. An **effector** organ—muscle or gland.

3. A **conductor** mechanism, composed of the afferent neurone, the motor or efferent neurone, any neurone or neurones which connect them centrally, and the inter-neuronic synapses.

From every segment of the cord there emerges on each side two nerve-roots, which soon unite to form a spinal root. Of these roots, one, the posterior, normally conveys impulses towards the cord, the other, the anterior, away from it (**Bell's law**).

Posterior root fibres, when they enter the cord, ramify and connect with other cells as follows (Fig. 45, p. 286):—

1. They arborise around posterior horn cells as soon as they enter.

2. They pass to the opposite side of the cord.

3. They arborise around anterior horn cells at the same level.

4. They arborise around cells of Clarke's column.

5. They form a tract running up and down the cord for a short distance and terminating in the substantia gelatinosa, a mass of grey matter which caps the posterior horns.

6. They enter the white matter to form the posterior columns. Here each fibre divides into an ascending and descending branch. The latter group pass a short distance down the cord and end by arborising around posterior horn-cells. The ascending branches pass upwards, terminating at various levels, the largest of them reaching the medulla, where they arborise around cells of the nucleus gracilis and nucleus cuneatus.

The **anterior root fibres**, with the exception of those destined to supply the visceral system, all arise from nerve-cells in the anterior horns.

It will thus be seen that the path of conduction from the receptor to the effector organ must involve at least two neurones, with the synapse between them. In point of fact, in most reflexes more than two are involved, since one or more neurones are intercalated between the posterior

fibre and the anterior fibre. Such intermediary fibres, since they are situated entirely within the cord, are known as *proprio-spinal*. They serve especially to connect the posterior fibre of one segment with the anterior fibre of another.

Conduction in the Reflex Arc

Conduction in a reflex arc differs from conduction along a nerve-fibre in the following respects:—

1. In its *slower speed*. Frog's nerve at 15° C. conducts at the rate of 3 cm. per σ ($\sigma = \cdot 001$ sec.). The flexion reflexion in the frog occupies 30 σ . Moreover, the rate of transmission varies with the intensity of the stimulus and differs in different reflexes.

2. In the tendency to *after-discharge*. In the reflex the effect often continues long after the cessation of the stimulus, this period of after-discharge increasing with intensity of stimulus.

3. In its *irreversibility*. Conduction occurs only from receptor to effector.

4. In its *liability to fatigue*.

5. In its *greater dependence upon oxygen*.

6. In its greater susceptibility to the action of *anaesthetics*.

7. (When the reflex response is rhythmic), in the want of correspondence between the rhythm of stimulation and the rhythm of effect. The rhythm of the scratch-reflex, for instance, is the same whatever the mode of stimulation.

8. In its *greater liability to summation*. Summation we have already seen in nerve-fibre—it is the effectiveness of frequently repeated stimuli each of which is ineffective singly.

9. In the *greater length of the refractory period*.

Tendon or Deep Reflexes

The question arises here whether the contraction of a muscle which occurs when its tendon is struck—the knee-jerk, for instance—is reflex or not. Clearly the spinal

cord is involved, since the jerk is abolished when the motor nerve has been cut. But it might be that the cord sends out a constant succession of impulses which keep the quadriceps muscle in a state of tonus, and that the jerk is the expression of a local irritability only present when the muscle is in tonic contraction. Against this view is the fact that while the cut peripheral end of the motor nerve to the quadriceps is being stimulated so as to keep the muscle in tetanic contraction, the knee-jerk cannot be elicited. In favour of the view that the knee-jerk is a true reflex is the fact that contraction of the quadriceps is accompanied by relaxation of the hamstrings.

It was once alleged that the knee-jerk could not be a true reflex, since its latent period was too short. But recent and more accurate estimations have shown that the time elapsing between the moment of stimulation and the moment of contraction is of the same order as in the case of actions known to be of a reflex nature. We are therefore justified in regarding tendon-reflexes as true reflexes.

Such being in general the nature of reflex action, it now remains to find out which of the morphological components is responsible for those characteristics of the reflex arc which distinguish it functionally from the nerve-fibre. It cannot be the nerve-cell (so-called), since we have no evidence of any alteration in character of a nervous impulse as it travels through the spinal ganglia. The functions of the cell-body have always been regarded as being to control the nutrition of the whole cell, including the fibres, and to serve as a junction or meeting-place of dendrites and axons.

Many of the features of reflex conduction resemble those of conduction from nerve to muscle: the irreversibility, the delay in transmission, the liability to fatigue, and the susceptibility to drugs. For this reason, as well as by a process of exclusion, we are driven to the

conclusion that just as the junction between nerve and muscle confers certain characteristics upon conduction, so the synapse or junction between the neurones exerts, but to a greater degree, its influence upon impulses passing through it. As to the physical nature of the synapse we have no definite information. Even if it be that the synapse is composed of fibrils uniting neighbouring neurones, conduction along these must be profoundly different from conduction along the nerve-fibre. Moreover, it is only by ascribing such an influence to the synapse that we can explain how reflexes are, singly and in combination, adapted so as to become purposive acts. This we shall now consider.

Inhibition—Reciprocal Innervation.—Among the visceral nerves there are some, stimulation of which causes a depression or even cessation of a pre-existing state of activity. Stimulation of the peripheral end of the cut vagus, for example, slows and even stops the heart. Increased activity in a nerve leads to diminished activity in the organ which the nerve supplies. Inhibition is seated peripherally. Throughout the skeletal system there is no instance of a peripheral nerve which, when artificially stimulated, causes relaxation of a contracted state previously existing. But when a muscle is made to contract reflexly the act is always accompanied by active relaxation of the antagonistic muscle. This is easily proved. If an extensor muscle is severed from its distal bony connection it undergoes lengthening when the flexion reflex is stimulated. The relaxation of the one muscle is as essential a part of the reflex as contraction of the other. It has the same time relations, the same tendency to after-discharge, and generally observes the same rules.

Instances of reciprocal innervation are also seen, at any rate in a crude form, in the visceral system. In the intestine, stimulation at a certain point causes contraction above and relaxation below. Here, as in the case of the vagus nerve, the mechanism is purely peripheral.

In the skeletal system the mechanism of inhibition and of reciprocal innervation is situated centrally. An active state in an afferent nerve is converted centrally into a

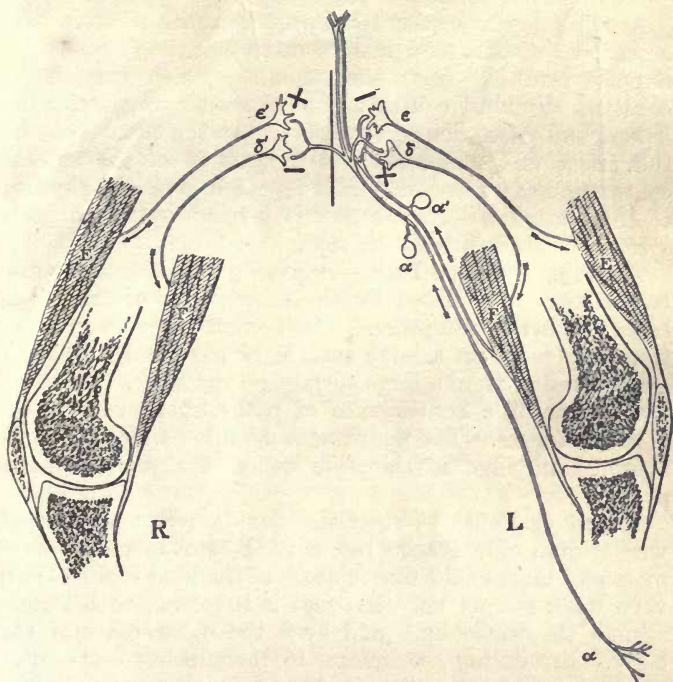


FIG. 44.—Diagram indicating connections and actions of two afferent spinal root cells a and a' in regard to their reflex influence on the extensor and flexor muscles of the two knees. The sign + indicates an excitatory and the sign - an inhibitory effect (Sherrington).

double effect—a positive effect upon one group of neurones and a negative effect upon another. Central inhibition is, however, not confined to the skeletal system. The depressor nerve arising in the heart and aorta inhibits a

pre-existing state of tonus of the blood-vessels. Respiratory movements are inhibited during the act of swallowing. In all these cases the conversion of a positive into a negative effect must be ascribed to the synapses.

Another degree in this transformation of a positive into a negative effect is seen in the scratch reflex. The nervous impulse resulting from the stimulus, which may be a constant stimulus, causes at one moment contraction of flexors and relaxation of extensors. At the next moment this effect is transformed into relaxation of flexors and contraction of extensors. This repeated gives the rhythm of the scratch. Such a reflex is termed by Sherrington a reflex of *successive double sign*.

The Final Common Path.—A given group of muscles can be brought into action by the stimulation of any of a large number of receptors. The flexion reflex is induced from any point on a large surface of the hind limb, the scratch reflex from a large surface on the back. There is, then, centrally a convergence of paths upon every group of motor nerves. The motor neurone upon which so many neurones impinge is therefore called the *final common path*.

Spread of Reflex.—When the flexion reflex is induced with stimuli of increasing intensity the movement involves more and more of the musculature of the hind limb. With very weak stimuli only the foot is involved, with strong stimuli the whole limb and even the other parts of the body. In addition, therefore, to there being centrally a convergence of paths there is also a divergence—a radiation from a central focus on the motor side. The spread of the reflex effect from the focus can only be explained by assuming that each afferent fibre comes into connection, directly or indirectly, with several motor cells, and that the synapses between the afferent fibres and the several anterior horn cells present to the afferent impulse varying resistances. Some of these resistances are forced easily, others only with difficulty.

Reinforcement and Combination of Reflexes.—When the scratch reflex is induced from two points situated close together on the skin the motor effect is more intense than if either stimulus acted singly. The two stimuli sum in their effect upon the final common path.

Antagonistic Reflexes—Interference.—Some reflexes are incompatible—the scratch and the flexion reflex, for example. If the flexion reflex is induced by a strong stimulus while the scratch reflex is in progress, the latter may be inhibited, the former taking its place. This is known as *interference*. Whether or no interference occurs, depends upon the relative strength of the stimuli causing the two reflexes. The cessation of one reflex and its replacement by another always occurs without delay and without confusion. One begins immediately the other stops. There is no intermediate period during which a composite, purposeless reflex occurs.

The Functions of the Cord

The grey matter of the cord forms the lowest member of the hierarchy of the central nervous system. Each segment governs the nervous reactions performed by that segment; in addition, the anterior horn cells govern the nutrition of the muscles which they supply. The segments of the cord are bound together functionally by tracts. On this account no reflex is confined to any one segment of the body. When an anterior root-fibre is stimulated the resulting movement is purposeless and inco-ordinate. The motor impulses which form a co-ordinated movement emerge by several roots. In this way certain segments of the cord are bound closely together—those for the upper limb form one group, those for the lower limb another. These sections of the cord have control over certain complex acts—not only skeletal movements but visceral functions—micturition, defæcation and parturition, all of which can, at any rate in lower animals, be performed when the cord is severed from the higher centres.

There remain certain functions which the cord alone cannot perform—willed movements and the psychical appreciation of sensory impressions. It is the function of the cord to convey these impulses between the higher centres and the periphery.

Lesions of the Spinal Cord in Man

After complete transverse lesions of the dorsal region, when the effects of shock have passed away a flexion reflex gradually develops. This becomes more and more easily elicitable, until a stage is reached when stimulation of any point causes strong flexion of both legs and contraction of the abdominal muscles. This is known as the mass-reflex.

Reflex micturition and defæcation are performed, the stimuli being distension of the bladder and rectum respectively.

Lesions of the dorsal region involving one-half of the cord lead to a condition known as Brown-Séquard Paralysis. It is characterised by—

1. Motor paralysis of the same side.
2. Slight vaso-motor paralysis of the same side.
3. Loss of sense of position and of passive movement on the same side.
4. Loss of touch, pain and temperature sensation on the opposite side.

PART IV

THE EXTEROCEPTIVE SYSTEM

THE following description of the higher centres is based upon Sherrington's division of the sensations into three main classes—*exteroceptive*, *proprioceptive* and *interoceptive*. We shall first consider the exteroceptive sensations—that is, those arising from changes in the outside world—and the manner in which the animal reacts to them. Secondly, we shall consider the proprioceptive sensations, or those which give impressions of bodily position, and the reactions which they induce. Finally, we shall deal with the interoceptive system, which relates to the gut and the structures derived from it.

The exteroceptive sensations are those changes in its surroundings to which the animal responds, which rise into its consciousness, and to which, if it is in a normal condition, it pays attention. They may be classified as follows :—

1. Those due to direct contact of a body with the skin (*cutaneous and deep sensation*).
2. *Light*.
3. *Sound-waves*.
4. *Chemical stimuli* produced by vapours of substances situated at a distance (*smell*), and by substances actually in contact with the mouth (*taste*).

These disturbances are appreciated because they stimulate certain nerves specially adapted to receive them. Each kind of sensory nerve conveys to the brain only one kind

of subjective sensation, in whatever way that nerve is stimulated. This applies not only to the nerve-ending but to the nerve-fibre. The optic nerve, however stimulated, only conveys a sensation of light; the auditory nerve only one of hearing. This is the **law of specific irritability**, first enunciated by **Müller**. The reason why normally a particular nerve only responds to a particular stimulus is partly because it is so situated in the body that only the appropriate stimulus can excite it, and partly because it is endowed with a higher susceptibility to that mode of stimulation than to all others.

Certain conditions materially affect the subjective sensation arising from a stimulus. One of these is the duration of the stimulus. The sense organs on prolonged stimulation become fatigued, and the resulting sensation becomes fainter. Another is the action of a previous stimulus. Hot water, for instance, feels hotter to the hand after cold. For these and other reasons sensations are never an accurate judge of stimuli. Attempts have been made to relate the intensity of the stimulus with the intensity of sensation, but the only law which is to any degree established is that of **Weber**, according to which the least increase in stimulus which can be appreciated bears a constant relation to the whole stimulus. If, for instance, a person can only just appreciate the difference between 10 grms. and 11 grms., he can only just appreciate the difference between 100 grms. and 110 grms.

1.—CUTANEOUS AND DEEP SENSATION

The three sensations which may be aroused by contact of the skin with an object are touch, pain and temperature. When an area of skin is carefully examined it is found that the appreciation of these sensations is confined to certain spots. There are spots for touch, for pain, for heat and for cold. These spots are bizarre in shape and distribution. Some overlap one another; others are separated by

patches of skin which seem to be totally insensitive. Each of these spots when stimulated causes but one kind of sensation, however stimulated; a cold spot touched with a hot object feels cold.

Touch.—The touch-spots are arranged especially around the roots of the hairs. Hairs considerably increase the sensitiveness of the skin to touch, by their leverage stimulating the nerve-endings which are in intimate association with their roots.

The number of touch-spots per unit area varies in different parts of the body, and with this is associated a corresponding variation in the power of accurately localising the point stimulated and of discriminating between one stimulus and two stimuli applied at the same time. The power of **discrimination** is greatest at the tip of the tongue, where two stimuli about 1 mm. apart are distinguished, least on the back, where two spots touched are not recognised as two unless they are about 70 mm. apart.

A rough estimation of the degree of sensitiveness to touch can be measured by means of **Von Frey's** hairs. These are hairs of different thickness mounted on handles. Knowing the pressure which just bends the hairs we can tell the pressure required to evoke a sensation.

Pain.—Pain is the affective aspect of a stimulus which is harmful and which therefore tends to evoke a protective motor response. The different kinds of pain are probably due to the coincident stimulation of other sense-organs. A tingling pain, for instance, would be caused by the coincident stimulation of pain- and touch-spots. Loss of sense of pain without loss of other forms of sensation is known as *analgesia*.

Temperature.—The sense of temperature is more acute in some parts of the body than in others. In general it may be said to be less acute on the exposed parts and in the mouth.

Several forms of nerve-endings are present in the skin.

There are the Pacinian corpuscles, Meissner's corpuscles, the end-bulbs, the nerve-plexus surrounding the hairs, and the free nerve-endings which ramify in the epithelium. Attempts have been made to identify each of these with some particular sensation. It is believed by some authorities that the corpuscles of Pacini and of Meissner are receptive to touch and the end-bulbs to temperature. It is natural to regard the nerve-plexus of the hairs as sensitive to touch. Pain is commonly held to be evoked by the free nerve-endings, the chief ground for this belief being that the cornea, in which these are the only nerve-endings present, is sensitive only to pain.

Deep sensation.—When an object is pressed against the skin with sufficient force to cause deformation of the skin, there is set up a complex of sensations, arising partly from the skin and partly from the deep structures, such as the muscles and their tendons. Our estimation of the texture, hardness and shape of objects is derived from an analysis of the combination of superficial and deep sensations.

Head, partly as the result of an experiment performed upon himself, showed that after section of a cutaneous sensory nerve recovery took place in two well-marked stages. In the first stage, which is usually fully established six months after section, pain of a burning, disagreeable character is felt, touch feels rough, and there is a crude form of temperature sense. Heat is only felt when above 38° C., and cold only when below 24° C. All the sensations are poorly localised and tend to radiate widely. This form of sensation Head terms **protopathic**.

In the second stage pain becomes more bearable and more definitely localised, the sense of touch becomes more delicate, while fine grades of temperature are appreciated. This form of sensation is known as **epieritic**. **Deep sensibility**, in which two elements are recognised, deep pressure and pressure pain, is not lost unless the motor nerves are

cut. Head therefore believes that in the nerve-trunks three forms of sensation are carried—protopathic, epicritic and deep.

For the investigation of the **Central Paths** taken by afferent impulses two methods have been used. The first is the examination of patients suffering from partial injury to the spinal cord. For touch and pressure this is, indeed, the only method, but for pain there is in addition a second method, based upon Sherrington's **Pseudoaffective Reflexes**. An animal is deprived of its cerebrum and a sensory nerve stimulated. It cannot, of course, feel pain, but the reflex arcs subserving the bodily expression of the emotions are intact. There are snarling movements of the face, movements of the limbs and an elevation of blood-pressure. The occurrence of these changes when a nerve is stimulated denotes that pain would have been felt had the cerebrum been present. Different columns of the cord are divided, and the effect upon the transmission of the sensory impulse noted.

Within the cord there is a complete regrouping of sensations. There is no longer a distinction between protopathic and epicritic, nor between superficial and deep sensations.

Sensations of light touch and deep pressure pass upwards on the same side for a variable distance, then cross over gradually and continue their upward course in the anterior columns. Arriving at the optic thalami, they are continued in a fresh relay of fibres to the cortex. The part of the cortex concerned is the pre-central (motor) area, and probably the adjacent post-central area. When these areas are irritated, tingling sensations are felt. Conscious sensations of passive movement are located in the motor area.

Sensations of pain and of temperature of all kinds are believed to decussate immediately on entering the cord and to pass up in the anterolateral region, eventually reaching the optic thalamus.

There appears to be no area in the cortex devoted to the reception of pain impulses. Irritation of the cortex in man never gives rise to pain, nor does stimulation in animals. According to Head, the optic thalamus is the centre for the reception of crude sensations of pain, and the cortex exercises over this centre an inhibitory effect. When the fibres between the cortex and the thalamus are

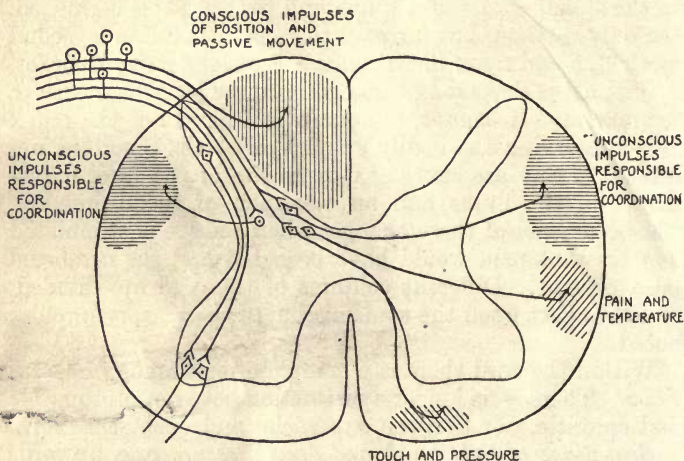


FIG. 45.—Diagram to illustrate the main connections of a posterior root and the transmission of sensations up the cord (after Page May).

destroyed there follows a condition, known as **thalamic over-reaction**, in which pain is felt to be abnormally intense and to have a disagreeable character. On this view the function of the cortex is to modify this crude sensation and to give it a discriminating and intellectual stamp.

2. VISION

The eyeball has three coats—from without inwards, the sclerotic (protective layer), choroid (vascular layer) and

retina (sensitive layer). The **sclerotic** is a firm membrane composed of white fibrous tissue lined externally and internally with a layer of endothelium. The internal endothelial layer contains a network of pigment cells (*lamina fusca*).

At the front of the eye the fibrous tissue of the sclerotic becomes modified to form the transparent **cornea**. The cornea has a smaller radius than the rest of the eye, and therefore forms a projection upon what is otherwise an almost perfect sphere.

In the cornea five layers are recognised: (a) stratified epithelium, continuous with the conjunctiva; (b) the anterior elastic layer of Bowman; (c) the substantia propria—this consists of laminae of connective tissue fibres arranged parallel to the surface and separated by cell-spaces or lacunae, in which lie corpuscles; (d) the posterior elastic layer of Descemet; (e) endothelium.

The cornea has no blood-vessels, its cells being nourished by a flow of lymph from peripheral blood-vessels. The surface of the cornea is kept clean by the tear-fluid secreted from the lachrymal gland.

The **choroid** is composed of three layers: (a) externally the lamina suprachoroidea, which contains pigment-cells; (b) the vascular layer, in which the blood-vessels form a rich anastomosis; (c) the membrane of Bruch.

In the anterior part of the eye the choroid is modified to form the **ciliary glands and muscles** and the **iris**.

At the ciliary glands the surface of the choroid is thrown into folds (**ciliary processes**), which afford attachment to the suspensory ligament of the lens. The ciliary glands secrete aqueous humour.

The ciliary muscles will be described later in connection with accommodation.

The **iris** forms a diaphragm having a central aperture. It is composed of three layers: (a) an anterior layer of endothelium, continuous with the posterior layer of the cornea; (b) a layer of fibrous connective tissue; (c) a

pigmented layer behind, continuous with the retina. In the middle layer are two muscles—**sphincter pupillæ**, whose fibres are arranged circularly, and the **dilator**, whose fibres

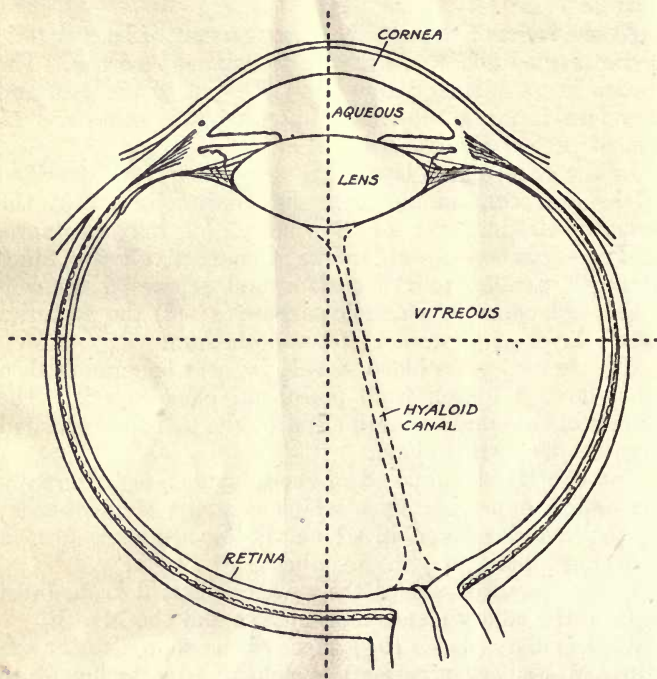


FIG. 46.—Transverse section through equator of left eye seen from above (from Starling's *Principles of Physiology*).

are arranged radially. Immediately behind the iris is the **lens**, biconvex in shape and having a high refractive index. It is supported by and enclosed in the suspensory ligaments. It divides the eyeball into two compartments, anterior and posterior. The anterior chamber is occupied by the fluid

aqueous humour, and the posterior by the semi-gelatinous vitreous humour.

The greater part of the aqueous humour, after being secreted by the ciliary glands, passes into the anterior chamber between the lens and the free margin of the iris. It leaves the anterior chamber by the *sinuses of Fontana*, situated near the attached border of the iris, and enters the *canal of Schlemm* (Fig. 47). The aqueous humour

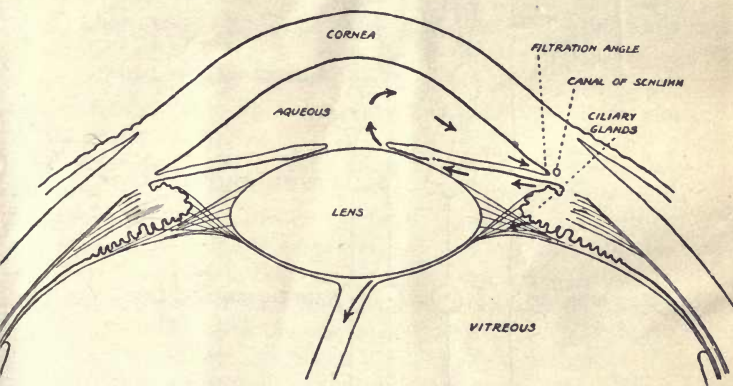


FIG. 47.—Diagram showing origin and fate of aqueous humour (Hartridge, from Starling's *Principles of Physiology*).

exerts a pressure of from 25–40 mm. of mercury (intra-ocular pressure).

The **retina** is composed essentially of the rods and cones and their nervous connections, these being supported by a scaffolding of connective tissue. It should be realised that the rods and cones are directed into the substance of the eyeball—that is to say, *away from the source of light, not towards it*, as might be supposed. The layers of the retina from without inwards are shown in the accompanying figure. It will be seen that the rods and cones abut distally against a layer of pigmented epithelium,

and centrally come into contact at the outer molecular layer with the first order of neurones—bipolar cells, which in

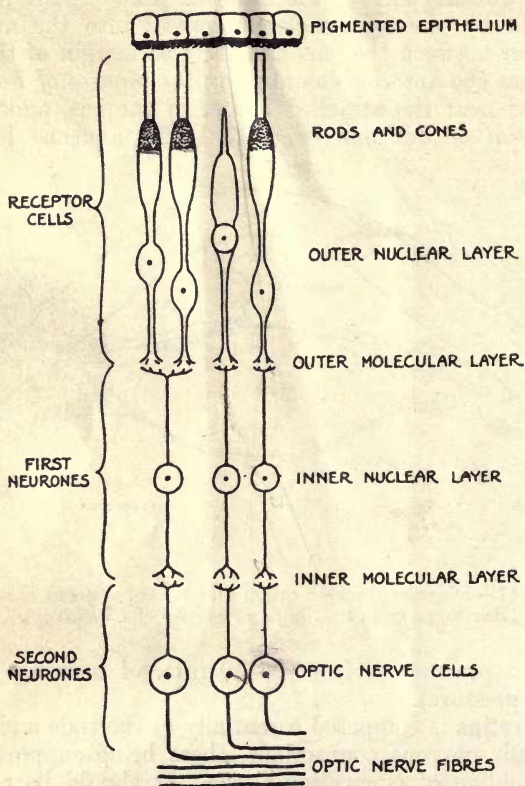


FIG. 48.—Diagram showing layers of retina.

turn are connected at the inner molecular layer with the dendrites of the optic nerve. Internal to this comes a layer of optic nerve-cells, and then the optic nerve-fibres.

Certain parts of the retina require special mention.

Opposite the pupil is the *macula lutea*, or yellow spot which surrounds a depression known as the *fovea centralis*. Here only cones are present, and each fibre of the optic nerve is connected only with one cone. This area is further distinguished by the fact that there are no optic nerve-cells or nerve-fibres directly beneath it, and that it is devoid of blood-vessels. At the periphery of the retina rods predominate. The fibres of the optic nerve converge upon a point (the blind spot) just internal to the yellow spot, where they pierce the choroid and sclerotic and form the trunk of the nerve. Here too there is a depression—the optic cup, from the bottom of which enter and leave the central artery and vein. At the optic cup there are neither rods nor cones.

Movements of the eyeballs are effected by the six ocular muscles. These are the superior, inferior, external and internal recti, which draw the eyeball upwards, downwards, outwards and inwards respectively; the superior oblique, which rotates the eyeball so that the eye looks outwards and slightly downwards; and the inferior oblique, by which the pupil is directed outwards and upwards. The lower motor nerve-centres for these muscles are situated in the grey matter surrounding the Sylvian aqueduct. Movements of the eye muscles can be induced by stimulation of several of the higher centres—notably the frontal lobe and angular gyrus of the cerebrum and the deep nuclei of the cerebellum. The movements thus induced always involve both eyes in such a manner that the axes of the eyes are parallel (**conjugate deviation**). This is owing to the intimate connection which exists between the mid-brain centres. Like the muscles of the limbs, the ocular muscles show reciprocal innervation, contraction of one muscle being associated with relaxation of its antagonist. Contraction of the left external rectus is accompanied by contraction of the right internal rectus and inhibition of the left internal and right external recti.

Voluntary movements of normal eyes are always con-

jugate when the eyes are focussed on distant objects. When near objects are looked at a certain amount of convergence takes place.

The muscles of the iris are controlled by two sets of nerves, the ciliary branches of the third cranial nerve which supply the sphincter pupillæ, and the sympathetic which supplies the dilator. These muscles are related to one another reciprocally, contraction of one being accompanied by active relaxation of the other.

Under normal conditions the pupil is **contracted** :—

1. When the eye is exposed to light. This is the *light reflex*, the afferent path being the optic nerve, the efferent being the third nerve. When any part of this arc is destroyed, *e.g.* by atrophy of the optic nerve, the light reflex fails. The purpose of this reflex appears to be to protect the retina from sudden changes in brightness.

2. During *accommodation* for near objects. In this way a sharper definition is obtained, owing to the cutting out of the rays from the periphery of the lens (*see later*).

3. During *sleep*.

The pupil is **dilated** (1) in the dark; (2) on focussing upon distant objects; (3) on sympathetic stimulation, whether due to a sensory stimulus or to an emotional state.

When the eye ceases to respond to light but can still accommodate the condition is known as the *Argyll-Robertson pupil*.

Action of Drugs

The following drugs contract the pupil :—

Opium and morphia, by stimulating the third nerve centrally;

Pilocarpine and physostigmine, by stimulating the third nerve peripherally;

while the following dilate it :—

Atropine, by paralysing the third nerve peripherally;

Adrenalin, by stimulating the sympathetic peripherally.

REFRACTION

The refractive power of the eye, by which rays of light are brought to a focus on the retina, is attributable to the cornea, aqueous humour, lens and vitreous humour. Of these the most important is the cornea.

Errors of Refraction.—**Hypermetropia**, or long-sight, is due in children to the eyeball being too small, owing to its having prematurely ceased to grow. Rays of light come to focus behind the retina. This error is corrected by the use of convex glasses. Hypermetropia also occurs in old age owing to failure of accommodation.

In **Myopia**, or short-sight, light comes to a focus in front of the retina. It is due either to the eyeball being too long or to the lens being too highly refractive. The former defect is due to deficient nutrition during the growing period and over-strain, the weakened eyeball being unable to withstand the intraocular pressure. It is for this reason that treatment should not only include the provision of concave glasses, but should also be directed to relieving the general condition.

Another error of refraction is **astigmatism**. This is due to the lens not having the same curvature in its horizontal and vertical axes. The consequence is that horizontal and vertical lines cannot be simultaneously focussed. For this defect cylindrical glasses are used.

ACCOMMODATION

When the eye is looking at a distant object the rays of light coming from that object are practically parallel. These in a normal eye come to a focus on the retina without any accommodation. Rays from a near object, however, diverge as they approach the pupil, and if no change took place in the eye would come to a focus behind the retina. To correct for this the eye undergoes the process of accommodation, which takes place in the following way.

The lens, being enclosed in an elastic capsule, always tends to assume a spherical form, but is prevented from doing so by the tension of the suspensory ligaments (due to the intra-ocular pressure), which attach it to the ciliary processes. The

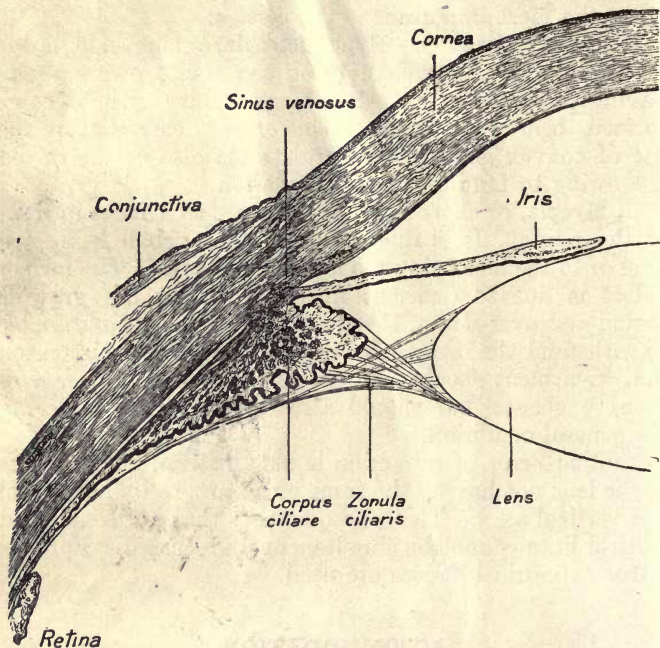


FIG. 49.—Anterior part of eyeball showing relation of iris, lens, ciliary bodies and corneosclerotic junction (from Starling's *Principles of Physiology*).

ciliary muscle consists of two parts: circular fibres which run round the eye at the corneosclerotic angle, and meridional fibres which pass backwards to be inserted into the ciliary processes. When this muscle contracts the circular fibres draw the ciliary processes as a whole into

a smaller circle, while the meridional fibres cause the ciliary processes to be drawn towards the pupil and slightly forward. The effect of contraction of this muscle is therefore to release the tension of the suspensory ligament and to allow the lens to become more spherical. The refractive power of the lens is in this way increased and divergent rays are focussed on the retina. The ciliary muscles are supplied by the third nerve.

Accommodation is always accompanied by contraction of the pupil. This results in a clearer definition of the image, owing to the cutting off of the rays which strike the periphery of the lens, and to the increased depth of focus.

The clearness of the image formed upon the retina is limited by **diffraction**—that is to say, the tendency of the edges of the wave of light to spread and form patterns. Diffraction is a physical process, and is therefore inevitable. There remain to be considered two other optical errors and the means taken by the eye to overcome them.

Chromatic Aberration.—The waves of short length (those at the blue end of the spectrum) are deflected by the refracting media more than the long red waves. The normal eye is so shaped that yellow—that is, the most intense—rays focus on the retina, red rays behind and green and blue rays in front. Around a central spot of yellow there are therefore formed a small halo of red, a small halo of green and a large halo of blue. The red and green halos combine to form yellow, while the blue is too diffuse to stimulate the retina.

Spherical Aberration.—If the refracting media were of uniform density and their surfaces of uniform curvature, rays striking the cornea peripherally would come to a focus in front of those passing centrally. This is obviated in two ways: (1) the centre of the lens is more highly refractive than the periphery; (2) the curvature of the anterior surface of the cornea is less peripherally than it is centrally.

PHYSIOLOGY OF THE RETINA

When light falls upon the retina certain changes take place which may be summarised as follows :—

Structural Change.—The cones shorten and the processes of pigment emerge from the epithelial layer to envelop the ends of the rods.

Electrical Change.—This occurs on darkening as well as on exposure to light.

Chemical Change.—In the ends of the rods is a purple pigment, **rhodopsin** or **visual purple**. It is bleached by exposure to light. The whole retina, too, takes on an acid reaction. The restitution of the rhodopsin is performed by the pigment cells.

It is believed that the cones respond to daylight and the rods to twilight vision, and that only the cones respond to colour. The evidence for such a distinction between the two elements is—(1) twilight vision is most acute at the periphery of the retina where rods are most abundant, and deficient at the fovea where only cones are present; (2) green rays, which are seen best of all colours at twilight, are those which are most effective in bleaching rhodopsin. Foveal vision further differs from peripheral in being more sharply defined.

The peripheral limit of retinal sensitiveness is determined by means of the perimeter. It is found that the extent of the visual field varies for different colours.

COLOUR VISION

Of the theories which have been put forward to explain colour vision, the following are the most important.

Young's Hypothesis.—On this view there are three different substances present in the retina, one responding to red, another to green, a third to blue. When these are stimulated simultaneously fusion in the brain leads to a sensation of white. Different colour sensations are due

to different combinations of the stimulated substances. Colour blindness on this view is due to the absence of one or more of these substances, or to abnormality in their absorption of light.

Hering's Hypothesis.—There are three substances present in the retina called red-green, yellow-blue and white-black. These are capable of being catabolised or anabolised. When, for instance, the red-green substance is stimulated by red rays it is built up into a more complex compound, while under the influence of green rays it is broken down. On this view colour blindness to red and green or to blue and yellow is due to the absence of the corresponding substance.

Edridge-Green's Hypothesis.—As in Young's view, three substances are present, responding to red, green and blue, but these are located in the brain.

THE PERCEPTION OF SIZE, SHAPE AND DISTANCE

When we look at an object with one eye we are dependent for our idea of its size, shape and distance upon our past experience. Into this several factors enter: (1) from our knowledge of the true size of the object we can gauge its distance; (2) from the intensity of light upon its different surfaces we can tell its shape; (3) from the apparent convergence of lines which we know by experience to be parallel we can judge how far the lines recede; (4) finally, from parallex—that is, the relative movement of distant and near objects as we move—we can estimate distance. It is not possible that the muscular movements concerned in accommodation give us a sensation of depth and distance.

With unocular vision this power of judgment would fail us if we were faced with conditions of which we had no past experience. Even when we look at familiar objects and scenes these always seem flatter to one eye than to both eyes.

Binocular perception adds a further method of judging distance. In animals such as man which have parallel optical axes the visual fields of the two eyes overlap to a considerable extent. Rays of light coming from any point in the common field of vision stimulate corresponding points on the two retinae, so that the two stimuli are fused centrally to form one visual impression. For instance, an object situated in front of another forms an image on the temporal side of the other on the left retina and an image on the nasal side on the right retina, yet these corresponding images cause but one image to be formed in consciousness. The images formed on the two retinae are thus not exactly the same, and it is the fusion of these slightly different images in the brain which gives us stereoscopic vision.

CENTRAL CONNECTIONS OF THE OPTIC NERVES

The two optic nerves join together at the optic chiasma, where a partial decussation takes place. The fibres from the nasal half of the retinae cross over, while those from the temporal half remain on the same side; fibres from each fovea being partly crossed, partly uncrossed. The regrouped fibres are conveyed by the optic tracts to the brain-stem, where they terminate in three nuclei, the *anterior corpora quadrigemina*, the *optic thalamus* and the *external geniculate bodies*. In the anterior corpora quadrigemina some fibres arborise round nuclei of the third and fourth cranial nerves; others arborise around cells which pass down the brain-stem in the posterior longitudinal bundle and thus bring the optic nerves into functional connection with the other cranial and the spinal nerves. This connection provides a means of co-ordination between visual impressions and the muscles of the limbs.

From the optic thalamus and external geniculate bodies there starts a fresh relay of fibres which pass through the posterior limb of the internal capsule to end in the occipital lobe in the anterior part of the calcarine fissure. Destruc-

tion of this area in man causes blindness to objects situated on the opposite side of the body—that is to say, there is

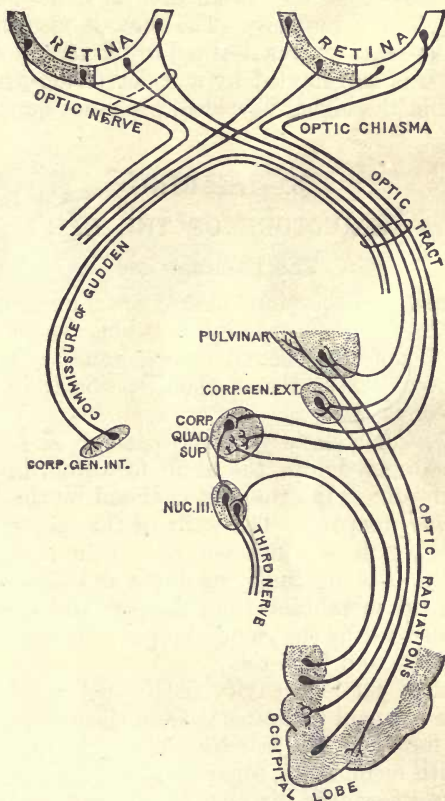


FIG. 50.—Diagram of connections of optic nerve (Cunningham).

an inability to appreciate objects whose images are formed on the temporal half of the retina of the same side and on the nasal half of the retina of the opposite side.

Stimulation over a wide area on the occipital lobe in the monkey causes movement of the eyes to the opposite side. It is probable that the visual area is more restricted in man than in the monkey. The view is also held that a small (**visuo-sensory**) area devoted to the reception of visual impressions is surrounded by a wider (**visuo-psychic**) area concerned in the higher psychical processes associated with vision.

3.—HEARING

STRUCTURE OF THE EAR

The External Ear

This consists of the pinna and external auditory meatus. The pinna in lower animals by its tubular shape serves the purpose of collecting sound-waves, and by its mobility enables the animal to detect the direction from which the sound is coming.

The *meatus* is a slightly curved passage, about one inch in length, directed into the skull forwards, inwards and slightly upwards. Internally it is closed by the *tympanum* or *membrana tympani*. The walls of the meatus are lined with skin, which is continued as a thin layer over the tympanum. The meatus by its depth and curvature serves to protect the membrane from damage and cold, and the cerumen secreted by the glands keeps it moist and protects it from insects and bacteria.

The **middle ear** is a cavity in the petrous bone. The *membrana tympani* separates it from the external ear, and two small foramina, the *fenestra ovalis* and *fenestra rotunda*, covered with membranes, separate it from the internal ear. By the *Eustachian tube*, directed downwards and backwards, it is in communication with the cavity of the pharynx. The opening of the Eustachian tube is normally closed except during the act of swallowing, when it opens. In this way the pressure on the two sides of the membrane is kept equal. When the tube is blocked by disease the air

within the middle is absorbed and the inequality of pressure thus produced causes deafness.

The tympanum is a thin elastic membrane covered

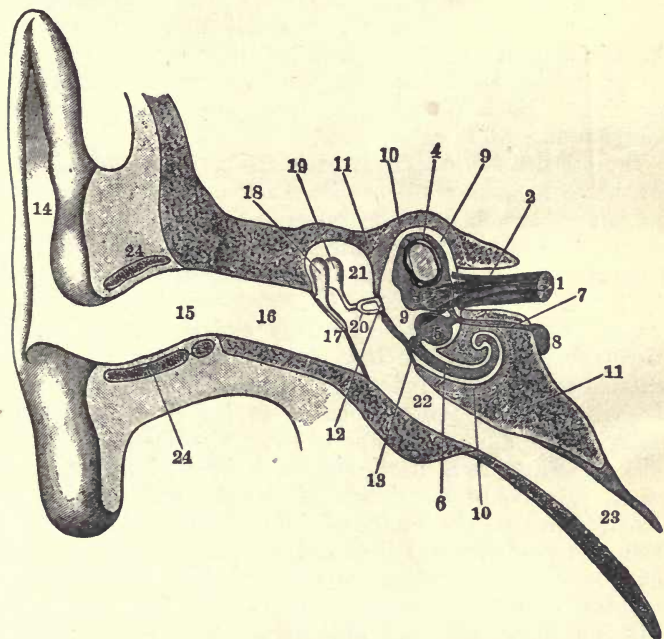


FIG. 51.—Auditory organ (diagrammatic, after Schafer): 1. Auditory nerve; 2. internal auditory meatus; 3. utricle; 5. saccule; 6. canalis media of cochlea; 9. vestibule containing perilymph; 12. stapes; 13. fenestra rotunda; 14. pinna; 16. external auditory meatus; 17. membrane tympani; 18. malleus; 19. incus; 23. Eustachian tube.

externally by skin and internally by mucous membrane. The fibres composing it are arranged circularly and radially. Along part of its inner surface is attached the handle of the *malleus*, the outermost of the three ossicles.

The function of the tympanum is to transform the vibrations of the atmosphere into mechanical movements. To perform this function adequately it must be aperiodic—that is to say, it must itself have no period of vibration. Owing to the pull of the tensor tympani on the malleus the tympanum is bell-shaped, its apex inwards. It is composed of a series of superimposed and gradually narrowing rings. Each ring has its own periodicity, but the bell cannot vibrate as a whole.

The ossicles form a chain of bones crossing the middle ear. The malleus consists of a head and two processes, the handle attached to the tympanum and the processus gracilis to the wall of the middle ear. The head of the malleus engages with a hollow surface on the next ossicle, the incus. The incus has a long process, directed downwards, articulating with the third ossicle, the stapes, a stirrup-shaped bone, the base of which is adherent to the fenestra ovalis. The function of the ossicles is to transmit the vibrations of the tympanum to the fenestra ovalis, and so to the fluid perilymph of the internal ear.

The malleus rotates through a horizontal axis which passes just below the heads of the malleus and incus. When, therefore, the handle of the malleus moves inwards the upper part of the malleus and incus move outwards and the process of the incus moves inwards. The inward movement is transmitted through the stapes to the fenestra ovalis.

It is believed by some authorities that in the ossicles a magnification of effect is produced owing (1) to the handle of the malleus being larger than the process of the incus, and (2) to the fenestra ovalis being only one-twentieth the size of the tympanum. It is probable that any effect of this kind is to a great extent discounted by the friction and inertia of the system.

Of the two muscles of the tympanic cavity the tensor tympani exerts a constant pull, as already stated, upon the membrane, and therefore keeps it taut. It is also said to influence by alterations in its tension the receptivity of

the membrane for high and low notes. When the membrane is stimulated the muscle undergoes reflex contraction. The view is also held that the tensor tympani protects the drum from over-stretching by allowing it to slacken when no sounds fall upon it.

The function of the stapedius is not known with certainty.

The Internal Ear

Embedded in the temporal bone is a system of canals, the *bony labyrinth*, part of which forms a spiral tube, the *cochlea*. Within the *bony labyrinth* is an inner system, the membranous labyrinth, composed of the saccule, utricle, semicircular canals, and a part within the cochlea known as the *scala media*. Both labyrinths are filled with fluid, that filling the bony labyrinth being called perilymph, that filling the membranous labyrinth, endolymph. The cochlea is the only part of the labyrinth with which we are now concerned. About 25 mm. in length, it is wound around a central pillar, the *modiolus*. From the *modiolus* a ledge projects into the canal of the cochlea throughout its course. This ledge is therefore known as the *spiral lamina*. From the outer edge of the spiral lamina two membranes stretch across the canal of the cochlea, dividing this into three parallel compartments, the *scala vestibuli* uppermost, the *scala tympani* lowest, and the *scala media* between. The *scala vestibuli* is separated from the *scala media* by the thin *membrane of Reissner*, and the *scala media* from the *scala tympani* by the *basilar membrane* and the structures situated upon it. At the blind end of the canal of the cochlea the basilar membrane is deficient, and *scala vestibuli* and *scala tympani* communicate. Both the *scala vestibuli* and *scala tympani* form part of the bony labyrinth and contain perilymph, and both are in connection through membranes with the middle ear, the former at the fenestra ovalis, the latter at the fenestra rotunda. The *scala media*, on the other hand, is, as stated

above, part of the membranous labyrinth and is filled with *endolymph*.

Upon the basilar membrane are the *two rods of Corti*, which lean together, so that with the part of the basilar membrane between them they form a tunnel extending all the way up the cochlea. *Leaning against the inner rod is a row of *hair-cells*, and external to the outer rod

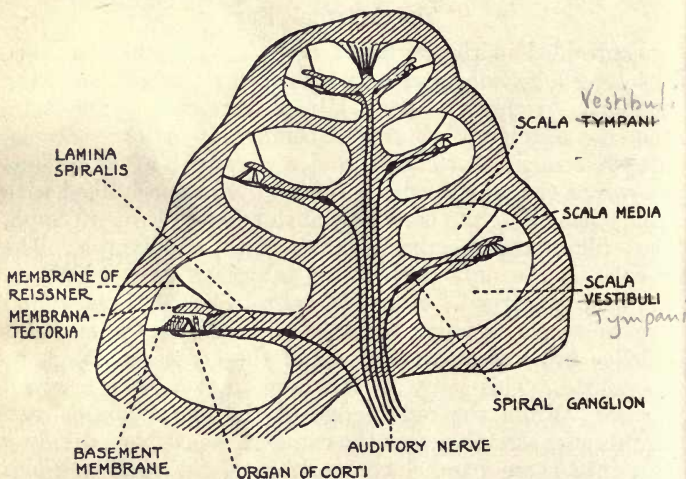


FIG. 52.—Diagrammatic vertical section through cochlea.

are several rows of the same, separated by sustentacular cells. The hair-cells are the peripheral end-organs of the auditory nerve, filaments of which reach them by passing up the modiolus and along the base of the spiral lamina. From the spiral lamina a projection known as the membrana tectoria overhangs the hair-cells so that its under surface either just touches or just fails to touch the ends of the hairs.

When the stapes drives the fenestra ovalis inwards the increase in pressure is communicated to the perilymph in

the scala vestibuli. This movement is transmitted through the membrane of Reissner to the endolymph and to the basilar membrane, and from these to the scala tympani, the result being a bulging outwards of the fenestra rotunda. It is usually believed that the auditory nerve is stimulated by vibrations of the basilar membrane, which cause the hairs of the hair-cells to move and possibly to touch the membrana tectoria.

As to the way in which sounds of different pitch are recognised, the most satisfactory hypothesis is that put



FIG. 53.—End-organ of the auditory nerve (from Starling's *Principles of Physiology*): B.M., basilar membrane; C., canal of Corti; R.C., rods of Corti; I.H., O.H., inner and outer hair-cells; S.C., sustentacular cells; Au., auditory nerve; m.t., membrana tectoria.

forward by **Helmholtz**, who regarded the basilar membrane as a series of resonators each responding to a certain periodicity of vibration. In favour of this view is the fact that when the short fibres of the membrane are degenerated, as in boiler-makers' disease, there is inability to hear high notes. In other conditions there may be deafness to some notes, not to others. Further, the ear can be fatigued to one note, leaving its appreciation of other notes unaffected.

CENTRAL CONNECTIONS OF THE AUDITORY NERVE

The cochlear division of the eighth nerve has its cell-body in the **spiral ganglion** of the cochlea. The axons of

though it were listening to a sound from the opposite side. Lesions of this area in man are usually found to be associated with deafness. In the monkey, however, both superior temporal lobes may be removed without causing any objective signs of deafness. It is believed, chiefly on histological grounds, that around this area of the brain, which forms a receiving station for stimuli (**audito-sensory area**), there is a large area, involving probably the whole of the temporal lobe, concerned with the higher psychical processes, such as the memory of sounds. This is the **audito-psychic area**. It is connected with the audito-sensory area by association fibres.

4.—SMELL AND TASTE

THE SENSE OF SMELL

Compared with some of the lower animals, man has but a poor sense of smell. Nevertheless his olfactory nerves are remarkably sensitive. The olfactory sense-organs are situated in the mucous membrane covering the superior turbinate bone and the part of the septum opposite. They take the form of bipolar cells, of which the free distal processes project slightly below the general level of the mucous membrane. Among these processes are the columnar sustentacular cells and the serous glands of Bowman, the latter serving to keep the sensitive nerve-endings moist. The proximal processes of the olfactory cells take the form of non-medullated nerve-fibres, which pierce the cribriform plate of the ethmoid and enter the *olfactory lobe*.

Here they terminate in a rich arborisation in close connection with the dendrites of the *mitral cells*, the arborisation of these two neurones forming the "*glomeruli*." The mitral cells, whose cell-bodies are also situated in the olfactory lobe, send axons into the fore part of the brain, where they make extensive and ill-defined connections with

the hippocampus, the posterior and inferior parts of the frontal lobe, and the gyri in relation to the anterior part of the corpus callosum. In animals in which the sense of smell is more acute these parts of the brain and the olfactory lobe itself are much better developed.

The olfactory epithelium is situated out of the direct line of the respiratory current. Air is diverted towards it in the act of sniffing.

The failure of some persons to recognise certain smells, and the fact that the nose may be fatigued to one kind of smell though retaining its sensitiveness to others, indicate that the sense of smell is complex, but no clear analysis of smells has yet been made. The sense of smell must be distinguished from other sensations arising in the nose, *e.g.* pungent sensations due to stimulation of the fifth nerve.

As regards the central localisation of olfactory sensation, the only experimental observations of positive value are those of Ferrier, who by stimulating the hippocampus induced movements of the nostril on the same side.

THE SENSE OF TASTE

Lying in the epithelium of the mouth are small bodies known as taste-buds. They are most plentiful around the circumvallate papillæ and upon the fungiform papillæ. A few are also found on the wall of the pharynx and cheek. The taste-buds contain the sensory nerve-endings of taste. These are spindle-shaped cells with free processes which project through the small orifice of the taste-bud. Among them are the columnar sustentacular cells. The taste-cells on the anterior part of the tongue are connected with the lingual branch of the fifth nerve and the chorda tympani, those on the back of the tongue with the glossopharyngeal. These nerves make widespread connections in the brain stem. The cerebral localisation of taste is not known.

Certain well-defined qualities of taste are recognised—salt, bitter, sweet, sour, alkaline, metallic. Some so-called tastes are in reality a combination of true taste sensation with smell and common sensation.

5.—MOTOR FUNCTIONS OF THE CORTEX

Having described the different sensations which play upon the cerebrum, we may now consider the motor aspect of this part of the central nervous system. Although the relationship between the cerebrum and the skeletal muscles had long been known from clinical experience and histological investigation and particularly from the work of Hughlings Jackson, it remained to Fritsch and Hitzig, in 1870, to demonstrate the connection experimentally. This pioneer work was afterwards amplified by many workers, particularly those of this country, Ferrier, Horsley, Schafer, Bastian, Sherrington and others. The principal part of the brain concerned in movement is the strip which lies immediately anterior to the *Rolandic* or *central fissure* (the *precentral* or *motor area*). Here all parts of the body are represented in order, from the toes near the middle line to the face laterally. An area on the third frontal convolution is concerned in conjugate movement of the eyes to the opposite side (Fig. 55).

The movements which are evoked by stimulation of any part of this area are confined to the opposite side of the body, except in the case of those movements in which muscles of both sides of the body normally take part, such as movement of the eyes, jaw and trunk. The movements are always co-ordinated and involve reciprocal action of antagonistic muscles.

When the motor area of one side is removed in the monkey the resulting paralysis is followed by a certain degree of recovery, but there is a permanent loss of finer accurate movements. The recovery is not due to education

of the opposite hemisphere, since no relapse occurs when the opposite side is subsequently ablated. Motor control appears to be taken over by the lower centres.

Irritative lesions of the motor area cause a peculiar kind of fit, known as **Jacksonian epilepsy**. The movement of

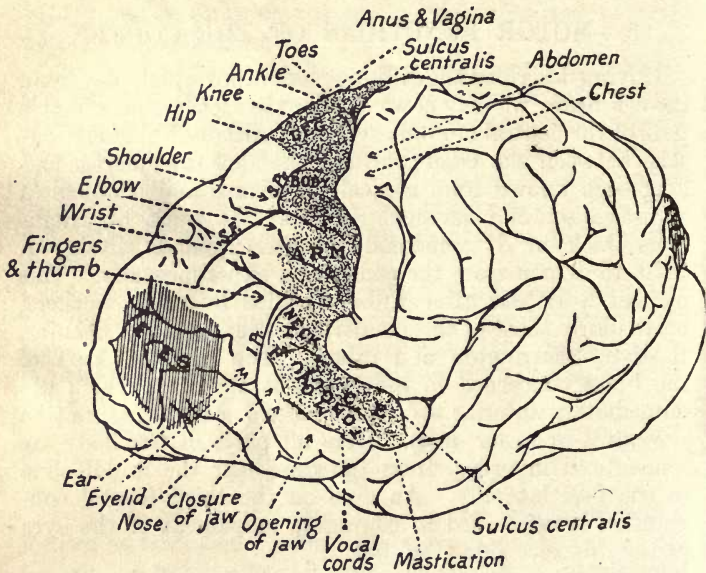


FIG. 55.—Outer surface of brain of chimpanzee, showing movements obtained by electrical stimulation (Sherrington).

the limbs is at first tonic, then clonic or rhythmic. The disturbance spreads from a focus to adjacent areas in the order of their proximity (the march of the fit), and in severe cases involves the whole side of the body and even the opposite side. Unlike ordinary epilepsy, the cause of which is unknown, Jacksonian epilepsy is usually not accompanied by loss of consciousness.

6.—SPEECH

A sound has three qualities : pitch, which depends upon the frequency of vibration ; intensity, which depends upon the amplitude of vibration ; and timbre or quality, which depends upon the relative proportions of the overtones.

The voice is produced by the vibration of the true vocal cords caused by the blast of air which is driven against them in expiration. The vocal cords are two parallel elastic membranes covered with mucous membrane and forming ridges which stretch between the thyroid cartilages in front and the anterior end of the arytaenoid cartilages behind, the two cartilages being separated by a cleft, the rima glottidis. The arytaenoid cartilages are capable of rotation on a vertical axis.

The size of the rima can be varied by approximating or drawing apart the posterior ends of the vocal cords. These movements are effected by adductor and abductor muscles respectively.

The principal abductors are the posterior crico-arytaenoids, which, arising from the posterior surface of the cricoid cartilage, pass upwards and outwards to be inserted into the outer angle of the arytaenoid cartilages.

The chief adductors are the arytaenoid muscles which pass from one arytaenoid cartilage to the other, and the lateral cricoarytaenoid which pass from the upper border of the cricoid to the outer angle of the arytaenoid.

The cords are put on the stretch by the cricothyroid muscle which passes from the cricoid cartilage to the inferior border of the thyroid cartilage. When it contracts the anterior part of the cricoid is drawn up and the posterior part drawn down.

The cords are relaxed by the thyro-arytaenoid muscles which run from the thyroid cartilage to the outer border of the arytaenoids, drawing the latter cartilages forward and also approximating the cords. Some of the fibres, forming a separate portion (*musculus vocalis*), are inserted into the cord itself. This has the effect of shortening the cords, and probably allows a part only of the cords to vibrate.

The **fundamental note** of a vocal sound depends upon the *tension* of the vocal cords. The **quality** of the sound depends upon the combination of overtones imposed upon the fundamental note by the resonance of the air passages. These include the pharynx, nasal cavity, laryngeal cavity, the cranial air-sinuses, and the trachea. The variations in quality are produced by alterations in

the shape of the resonator through movements of the cheeks, lips and tongue.

Consonants are produced by resisting the passage of air after it has passed the vocal cords. This may take place at the tip of the tongue and lips (dentals), between the tongue and the hard palate (labials), and at the fauces (gutturals). Explosives (*p, t, k, b, d, g*) are formed by the sudden release of resistance; aspirates (*f, s, l, sh, v* and *z*) by passing the air through a small slit; *m* and *n* by nasal breathing.

In whispering, the vocal cords do not vibrate, the sounds being produced entirely in the mouth.

The Central Mechanism of Speech

It is probable that the development of the power of speech in the human race occurs, as in each civilised child, in three stages. (1) *The cry*. This is used to express the emotions, and in lower animals to make signs of warning. The cry is probably represented centrally in the lower part of the brain, since Goltz's dog, which had been deprived of both cerebral hemispheres, was able to snarl, bark and growl. Its doing this to friend and enemy alike showed that it was ignorant of the significance of the sounds it made. (2) *Vocalisation*. This is the production of simple vowel sounds. It is believed to be represented bilaterally in the cortex. (3) *Articulation*. This develops with the growth of intelligence.

The power of speech is closely associated with the use of the hands, in gestures among primitive and in gestures and writing among civilised races.

Speech is a means of forming auditory symbols, and graphic records are a means of forming visual symbols for objects and ideas. The child learns to talk through hearing sounds. It then acquires the habit of imitating these sounds, and finally it learns to associate with certain visual images the sounds which others make and which it copies. When the name of an object is pronounced to an adult a complex mental process is set going—an auditory image, the corresponding visual image, and memories and associations connected with his past experience of the

object. The same processes must be working when he himself speaks or writes the name of the object. In such a complicated process as this it is clear that the brain must act as a whole. Nevertheless there appear to be certain regions of the brain which seem to be specially concerned in the production of the spoken and written word.

In 1863, **Broca** showed that loss of speech was produced by lesion of the third frontal convolution on the left side in right-handed and on the right side in left-handed people. These patients have lost the power of articulation. They can express themselves in writing and can hear and understand what is said to them and what they read. This condition is known as **motor aphasia**, and the centre which is diseased is known as the glosso-kinæsthetic centre, for it is the area supposed to be concerned in the sensation of the position and movement of the tongue. It was pointed out, however, by **Marie** that aphasia may occur without demonstrable lesion of this area. He believes that in the cases quoted by Broca the lesion was not limited, as was supposed, but involved subcortical fibres in such a way as to interrupt impulses coming from other parts of the cortex. Marie believes that there is no localisation of speech. In a sense this is true, but it might be expected that the power of speech would be more intimately associated with those areas of the brain concerned in the reception of images. Of these there are two—the auditory and the visual. The former is the centre concerned in the reception and storage of auditory words; it is situated in the temporal lobe. The latter is concerned similarly with visual words, and is situated in the occipital lobe. Above Broca's area, too, is an area in which the sense of movement of writing is said to be located. This area is adjacent to the part of the motor area devoted to the hand. It is therefore to be expected that a disturbance of any of these centres may cause loss of speech, and there is a certain amount of

clinical evidence to support this view. Cases have been described in which the spoken word is not understood (**word-deafness**). In these cases reading may not be impaired; the motor functions of speech may not be seriously disturbed. The loss of speech is due to an inability to hear and to form mental (auditory) images of words. This is one form of sensory aphasia. It is associated with a lesion of the temporal lobes. Cases of **word-blindness** also occur, but these are not associated with aphasia to the same extent, since auditory images are more important than visual images for speech.

The inability to write when it is unaccompanied by paralysis of other hand movements is known as **agraphia**.

The close connection which exists between speech and the more complex mental processes is shown by the fine distinctions in the disability found among different sufferers from aphasia. Some cannot state the names of objects, others cannot describe what the objects are for; in others there are certain particular words which have dropped out of their vocabulary. Others, again, are capable of emotional but not of intellectual expression.

LOCATION OF THE HIGHER PSYCHICAL PROCESSES

In its higher psychical function the cerebrum seems to act as a whole, the claims of the phrenologist being without scientific foundation. The only suggestion that any kind of localisation prevails comes from the examination of people suffering from injuries to the frontal lobes. Such patients often show a curiously facile behaviour, and seem to have lost the capacity for taking things seriously.

7.—THE FUNCTIONS OF THE CEREBRUM

The dominance of the cerebrum over the rest of the nervous system increases as we rise in the animal scale.

Goltz's dog, from which the cerebral hemispheres had been removed, was able to perform all movements, though in a clumsy manner. Its sensations were not impaired. It snarled and growled, but did so to friend and foe alike. It had no memory, and was only induced to eat when food was pushed up close to its nose. In the dog, then, the functions of the cerebrum are principally psychical.

The higher in the scale the animal is the more do motor and sensory functions come to be located in the hemispheres.

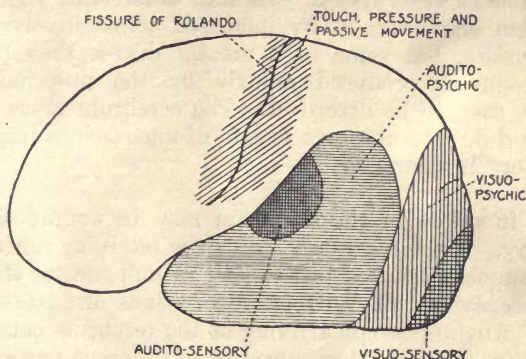


FIG. 56.—Principal sensory centres of the brain.

These functions have already been described, and their location will be readily understood from Figs. 55, p. 310, and 56, p. 315. One further word is necessary. We have seen that the reflex arc, as it travels through the cord, involves at least two and probably three neurones. It enters the cord as a sensory impulse and leaves it as a motor impulse. Where centrally the change from sensory to motor occurs it is impossible to say. Now sensori-motor reactions involving the brain also form a reflex arc, distinguished from a simple spinal arc only by the greater length of its path and the greater complexity of its connections. When, therefore, a motor reaction follows

artificial stimulation of the cortex it is not always possible to say whether the part stimulated is sensory or motor. The latent period of the reaction gives us some clue, a long latent period indicating that the part stimulated is sensory, the stimulus calling up a sensation which evokes a response. In other words, the cortex forms, as it were, a rounded summit to the arc.

When the cerebrum is disconnected from the remainder of the nervous system by section through the mid-brain the whole skeletal system goes into **decerebrate rigidity**, a condition characterised by increased tonus involving all the muscles, but some to a greater degree than others. This tonus is produced reflexly by the proprioceptive system, soon to be described. The cerebrum must therefore send down a constant stream of unconscious impulses, inhibitory in character.

The functions of the cerebrum may be summarised in this way. The cerebrum contains the receiving centres for those impulses aroused by external stimuli and for the *conscious* sensations of the relative positions of parts of the body. Any impression arriving at the cerebrum causes, on account of the free interconnection of different parts of the cortex, a more varied and more diffuse, and therefore more complete, response than can occur in the spinal animal. In addition, impressions which reach it tend to stamp upon it a more or less permanent record in the form of memory, and the animal is able to modify his reaction to an external stimulus according to his past experience—that is, according to the accumulation and association of his previous impressions.

Stimuli of a painful character tend to be more indelibly stamped upon the brain than those which are indifferent, owing to the fact that the former are accompanied by a subjective state known as an emotion. The human cerebrum is the seat of emotional feelings, of intellectual processes and of consciousness itself. The cerebrum, in

Sherrington's words, is the head-centre of the enterceptive system. It presides over the reactions of the body to its environment, restrains the lower centres and forms out of the primitive reflexes a co-ordinated response which past experience shows to be the most efficient under the circumstances.

PART V

THE PROPRIOCEPTIVE SYSTEM

By the proprioceptive system is meant the mechanism which is concerned in the transmission and reception of impressions which arise in the organism as the result of changes in its relation to the environment and of changes in the relative positions of parts of the body. The decerebrate animal, when suspended, adopts a certain posture, the limbs being partly flexed, different muscles being in a different state of tension or tonus. When the posterior roots are cut this state of tonus is at once abolished, the position of the limbs being now determined by gravity alone. As this effect is not produced when the cutaneous sensory nerves are cut, the afferent impressions which give rise reflexly to tonus must arise in the deeper structures—in the joints and in the muscles themselves. The intact animal is aware of the position of his limbs and of any changes in position which his limbs undergo.

The afferent nerves arise as extensive arborisations surrounding the tendons and bundles, and as branches which are entwined around certain of the muscle-fibres. The latter structures are known as **muscle-spindles**. Conscious sensations of position and of passive movement pass, as already described, to the motor area of the cerebrum. Unconscious impressions, as we shall see, pass up to the cerebellum.

THE LABYRINTH

While the afferent impulses from muscles and joints give us information regarding the position of our limbs, by other

impressions we are made aware of the position of the body as a whole and of the head in particular, in relation to the outside world. These impressions arise partly in the labyrinth, the end-organ of the vestibular branch of the *eighth nerve*. The labyrinth consists of a system of passages within the temporal bone (osseous labyrinth). Within the osseous labyrinth, and separated from it by a membrane, is an inner system, the membranous labyrinth. The osseous labyrinth is filled with perilymph and the membranous with endolymph. The labyrinth contains, in addition, the cochlea, but we are here concerned only with that part of the membranous labyrinth from which the vestibular branch of the eighth nerve arises. This part consists of two sacs, the *utricle* and *saccul*, which are connected together by a tube, the *sacculus endolymphaticus*, and the three *semicircular canals*. The **utricle** and **saccul** are two small sacs, into which open, from a projection on its wall, a number of hairs which are the terminations of some of the fibres of the eighth nerve (Fig. 51, p. 301). Among the hairs are a few calcareous nodules, the **otoliths**.

In lower animals, notably the crayfish, the otolith organ is cup-shaped, the hairs pointing inwards. In these animals the otolith can be removed and a small piece of iron inserted in its place. When a magnet is then brought near the head the equilibrium of the animal is disturbed. This experiment suggests that the otolith organ in the crayfish and, by analogy, the saccul and utricle in higher animals serve to give the individual information regarding the position of the head in relation to gravity. For any position of the head the weight of the otolith falls in a particular manner on the hairs, and this is interpreted centrally as a sensation of position.

The three **semicircular canals**, which are continuous with the cavity of the utricle, are disposed in three planes at right angles to one another, one horizontal and two vertical. Of the two vertical canals, the anterior canal of the one side lies in the same plane as the posterior

canal of the other. At one end of each canal is a dilatation, where is situated a hair-structure resembling those of the utricle and saccule, but without otoliths.

When the horizontal canals are destroyed on both sides there follow continual movements of the head in the horizontal plane, a condition which lasts a considerable

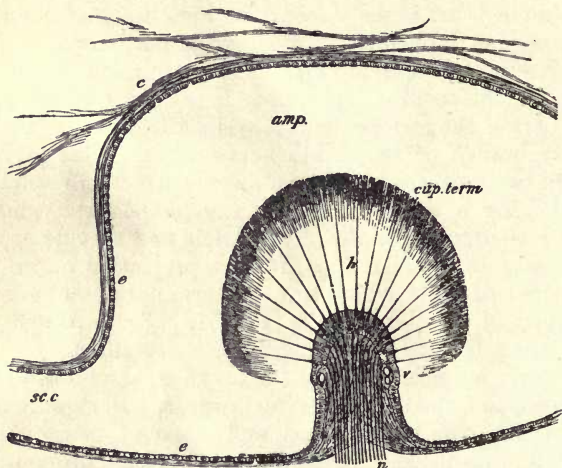


FIG. 57.—End-organ in ampulla of semicircular canal (from Starling's *Principles of Physiology*): *sc.c.*, semicircular canal; *h.*, hairs; *amp.*, ampulla.

time. When the canals on one side are destroyed there follows, in addition to disorders of equilibrium, considerable loss of tone on the same side of the body.

When in the bird the canals are destroyed on both sides the animal loses all sense of equilibrium, and performs violent and perpetual somersaults. After a prolonged period it recovers in some degree. This is owing to the education of other senses, chiefly the eyes, for when the partially recovered bird is blindfolded it reverts to

the condition which existed immediately after the operation. In the re-education of the sense of equilibrium the central region concerned is the cerebral cortex, for when this is removed from the animal which has to some extent recovered its equilibrium a permanent relapse ensues. No disturbance of equilibrium follows excision of the cerebrum when the labyrinth is intact.

How the canals act is shown by the classical experiment of **Ewald**. Ewald bored two holes into one of the canals and induced movements of the fluid by blowing into one or other of the holes. The head was always moved in the plane of the canal and in the direction of the current. The terminations of the eighth nerve in the hairs of the ampullæ are therefore stimulated by movement of the endolymph relative to the canal, such relative movement being due to the inertia of the fluid. This is why giddiness occurs, particularly when rotation is suddenly stopped. Some deaf mutes in whom the semicircular canals are imperfectly formed do not feel giddiness when rotated.

CENTRAL CONNECTIONS OF THE VESTIBULAR NERVE

The cell-bodies of the vestibular nerve are situated peripherally and form the *ganglion of Scarpa*. The axons entering the brain-stem deep to the restiform body (Fig. 58) divide into ascending and descending branches. The descending branches pass downwards into the medulla. The ascending, which are the more important, arborise around (1) the principal vestibular nucleus, (2) the **nucleus of Deiters** and **nucleus of Bechterew**, large cells situated in the outer part of the floor of the fourth ventricle, and (3) the nucleus fastigii of the cerebellum. By the nuclei of Deiters and of Bechterew they come into contact (a) with the cranial nerves by the posterior longitudinal bundle, and (b) with the spinal nerves by the vestibulo-spinal tract.

The chief connections of the nerve are, however, with the cerebellum.

VISUAL SENSATIONS

Among the sensations by which the animal is made

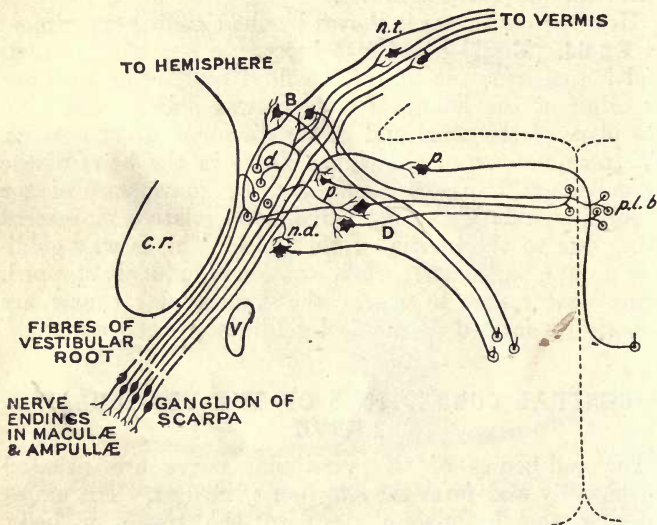


FIG. 58.—Connections of the vestibular division of the eighth nerve (from Schafer's *Essentials of Histology*): *c.r.*, restiform body; *V*, descending root of fifth nerve; *p.*, principal nucleus of vestibular root; *d.*, descending vestibular root; *D*, nucleus of Deiters; *B*, nucleus of Bechterew; *n.t.*, nucleus fastigii of cerebellum; *p.l.b.*, posterior longitudinal bundle.

aware of its own movement are those arising in the eyes. The optic nerve at the anterior corpora quadrigemina comes into connection with the cerebellum by the superior peduncles, and with the spinal nerves by the posterior longitudinal bundle.

THE CEREBELLUM

The cerebellum consists of a middle lobe, called the vermis, and two lateral lobes. The grey matter upon its surface is divided into two layers, an outer molecular layer composed of interlacing fibres, and an inner granular layer of small nerve-cells. At the junction of these layers are situated the cells of Purkinje, large cells whose axons pierce the subjacent white matter to terminate in the deep nuclei of the cerebellum. The latter are four masses of nerve-cells, the *nucleus dentatus*, *nucleus emboliformis*, *nucleus globosus* and *nucleus fastigii*. By its three peduncles the cerebellum makes the following connections:—

Afferent Tracts:—

1. With the spinal cord, by uncrossed fibres arising in the cells of Clarke's column travelling up (a) in the direct cerebellar tract, inferior peduncle, and terminating in the vermis; (b) in the indirect cerebellar tract, reaching the vermis by the superior peduncle.

2. With the medulla, and thus indirectly with the spinal cord, by fibres arising (a) in the nucleus gracilis and nucleus cuneatus; (b) in the olive. These fibres pass up by the inferior peduncle and are chiefly crossed.

3. With the vestibular nerve.

4. With the pons, by fibres arising in the nucleus pontis, crossing the mid-line, and terminating in the cerebellar cortex. Through these the cerebellum comes into connection with the cerebral cortex of the opposite side.

5. With the mid-brain, by fibres from the anterior corpora quadrigemina. This tract gives connection with the optic nerves.

Efferent Tracts.—These arise in the deep nuclei.

1. Fibres from the nucleus dentatus passing by the superior peduncle to the red nucleus and optic thalamus of the opposite side.

2. A few fibres to the nuclei pontis of the opposite side.

3. Fibres from the nucleus dentatus to Deiters' nucleus, from which arises the vestibulospinal tract of the same side.

Removal of the Cerebellum.—When one half of the cerebellum is removed and sufficient time has elapsed to allow the effects of irritation to pass away, the following condition occurs :—

1. Slight weakness on the same side (*asthenia*).
2. Loss of muscular tone on the same side (*atonia*).
3. Tremors on performing voluntary movements on the same side (*astasia*).

The animal is at first unable to walk, and lies down curled towards the side of the lesion, with the eyes directed to the opposite side. After several months it learns to stand, first by buttressing itself up against a wall. Later, it gains the power of walking in a modified way (drunken gait), the legs being abducted so as to overcome the tendency to fall over on the affected side. The recovery is due to the re-education of the motor area of the cerebrum, for when this is subsequently removed on the side opposite to the cerebellar lesion, the animal reverts permanently to its former condition.

When the cerebellum is completely removed the condition is in reality intensified, though owing to the symmetrical nature of the disorder it may be apparently less severe.

Cerebellar Lesions in Man.—In unilateral lesions the same symptoms are produced as after removal in animals—asthenia, atonia and astasia. Disturbance of equilibrium is shown in the gait, which is reeling, as that of a drunken man. Movements are slow, executed inaccurately, with a tendency to over-action. In walking, for instance, the feet are raised unnecessarily high (hen-gait). Speech is often affected, becoming slurred. On looking to one side, particularly to the side of the lesion, the eyes, owing to the muscular weakness, do not remain steady but tend to

return to the normal position. There result clonic movements, in which both eyes take part synchronously. This condition is known as *nystagmus*. There is no conscious loss of muscle sense—that is, sensation of position or of passive movement. Whatever impressions pass into the cerebellum are therefore unconscious.

Stimulation of the Cerebellum.—When the cortex of the cerebellum is stimulated, movements are only induced when strong currents are used. It is therefore believed that the cortex is inexcitable, the effects produced on strong stimulation being due to spread of the current. When the deep nuclei are stimulated, movements concerned in preserving equilibrium follow, particularly those of the head and eyes.

It will be seen that the afferent nerves from the muscles and joints and the vestibular nerve have this in common—that the impressions arising in them contribute reflexly to the maintenance of tonus, upon which posture depends. There is, again, a close similarity between the effect of destruction of the labyrinth and of removal of one lobe of the cerebellum. In both cases there is a loss of tonus on the same side of the body; in both cases a certain degree of recovery follows, owing to education of the cerebrum.

From the receptor organs of the muscles arise *conscious* sensations which give us information regarding the position of the limbs. From the labyrinth arise conscious sensations as to the relation of the body to its environment. These conscious sensations are located in the cerebrum. *Unconscious* impressions from the afferent spinal nerves play upon the centres of the cord and those from the labyrinth upon the cells of the medulla, in particular the nuclei of Deiters and Bechterew. It is the function of the cerebellum to analyse these impressions and to originate from them impulses which have for their object the maintenance of a condition of equilibrium and stability. By

its connection with the cerebrum of the opposite side and with the vestibulo-spinal tract of the same side it steadies the voluntary impulses from the cerebral cortex.

In any reaction of the body the part which the proprioceptive system plays is always secondary. An external stimulus causes a certain motor response. This motor response stimulates the proprioceptive nerve-endings. It is the proprioceptive system which the cerebellum dominates.

Summary of Functions of the Lower Centres

The *corpus striatum*, composed of the lenticular and caudate nuclei, is said to contain a centre for heat-regulation (p. 251).

The *optico thalamus* is believed to be the centre for the reception of crude afferent sensations. It is in contact with nearly all sensory nerves, especially with those from the eye, and with the cortex cerebri.

The *red nucleus* in the mid-brain is the head of the rubro-spinal system. It is connected also with the cerebellum.

The *pons* is a junction between one cerebral hemisphere and the opposite lobe of the cerebellum.

In the *medulla* are the vaso-motor and respiratory centres. It contains the nuclei of the vagus and hypoglossal nerves. Here enters also the eighth nerve. The *nucleus of Deiters* connects the cerebellum, the vestibular nerve and the spinal cord.

The function of the *olive* is unknown.

PART VI

THE AUTONOMIC SYSTEM

THE autonomic system is that part of the nervous system which supplies organs which are not under the control of the will. If we regard the primitive animal as being composed of two tubes lying one within the other, the autonomic system is that which is supplied to the inner tube (the gut) and its diverticula.

The disposition of the autonomic system will be more readily understood if the following points be borne in mind :—

1. The fibres of this system issue from the central nervous system in three situations—

a. From the brain stem, accompanying certain of the cranial nerves. This is the **cranial autonomic**. (*Culbar outflow*)

b. From the region of the cord which lies between the cervical and lumbar swellings (*thoracico-lumbar outflow*). *The fibres issuing here, and these only, are the sympathetic.*

c. From the sacral region of the cord (**sacral autonomic**).

These three regions are therefore separated by two regions of the cord from which no autonomic fibres issue. These are the cervical and lumbar swellings, which are devoted entirely to the skeletal innervation of the limbs.

2. The general distribution of the autonomic system is as follows—

The cranial autonomic supplies the pupils, the salivary glands and their blood-vessels, the heart and lungs, the alimentary canal and its diverticula down to the lower end of the small intestine. Also the kidney and spleen.

The sacral autonomic supplies the lower end of the gut and the organs of reproduction, with the exception of the uterus.

The sympathetic supplies (a) the gut, with its diverticula, from the cardiac orifice of the stomach to the rectum; (b) all the arterioles of the body, except those of the brain and heart; (c) the hairs and sweat glands of the skin; (d) the pupil and salivary glands; (e) the urino-genital organs.

3. As a general rule, to which, however, there are some exceptions, an involuntary organ is supplied by nerves from two sources: (a) the sympathetic; (b) the cranial or sacral autonomic. The organ is usually capable of activity independently of both these nerves. The two nerves serve, the one to increase its activity, the other to decrease it. The cranial and sacral autonomic have the effect of exalting digestive and reproductive functions; the sympathetic, while it depresses these functions, adjusts the animal to a condition of defence or offence.

4. Between its exit from the central nervous system and its destination the nervous impulse passes through one cell-station, and one only. This rule, to which no exception has yet been found, is known as **Langley's law**. A fibre which issues from the central nervous system (*pre-ganglionic fibre*) is invariably medullated, and in the case of the sympathetic is known as a *white ramus communicans*. The distal fibre with which this communicates (*post-ganglionic fibre*) is invariably non-medullated. The arborisation between the terminal filaments of the pre-ganglionic fibre and the nerve-cell of the post-ganglionic fibre can be identified by nicotine, which blocks conduction at the synapses. It takes place in one of three situations: (a) in the ganglia of the sympathetic (*lateral chain*); (b) in the great ganglia situated upon the abdominal aorta and its branches (*collateral chain*), and (c) peripherally in the organ itself (*terminal ganglia*).

It follows from what has been said that certain fibres may pass through a ganglion without interruption. The

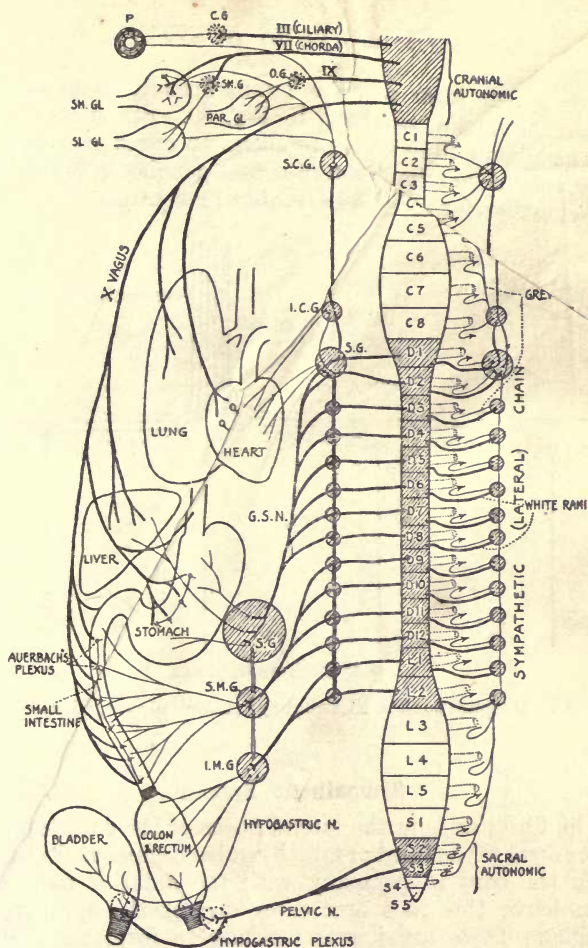


FIG. 59.—Autonomic system (diagrammatic). On the right are shown the white rami and the grey rami which join the spinal (somatic) nerves. On the left are shown the fibres which supply the viscera: P., pupil; C.G., ciliary ganglion; SM.G., submaxillary ganglion; O.G., otic ganglion; SM.GL., submaxillary gland; SL.GL., sublingual gland; PAR.GL., parotid gland; S.C.G., superior cervical ganglion; I.C.G., inferior cervical ganglion; S.G., stellate ganglion; G.S.N., great splanchnic nerve; S.M.G., superior mesenteric ganglion; I.M.G., inferior mesenteric ganglion.

fibres which form a white ramus usually terminate at different ganglia, as shown in Fig. 60. Stimulation of a pre-ganglionic fibre always produces an effect over a wider area than does stimulation of a post-ganglionic fibre. The ganglia therefore serve as distributing centres.

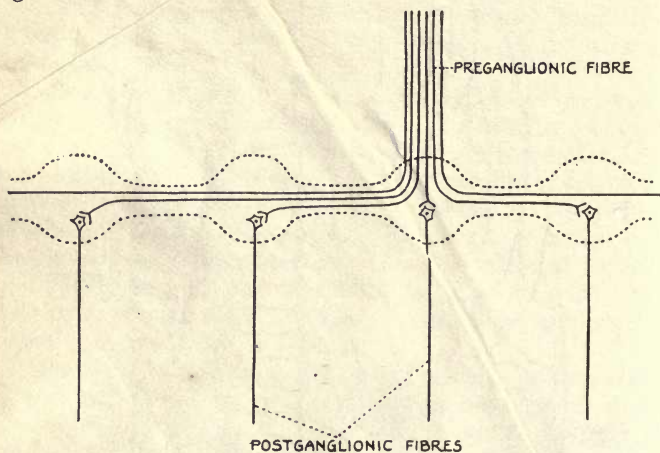


FIG. 60.—Diagram to show distributing function of sympathetic ganglia.

Sympathetic System

The fibres arise in the lateral horns of the cord from the first dorsal to the third or fourth lumbar segment. Emerging from the cord in company with the anterior root, they soon leave this root and enter one of the sympathetic ganglia. These are joined together to form the sympathetic or lateral chain which runs through the whole length of the trunk and is continued upwards into the neck. Some of the fibres, after passing for a variable distance up and down the chain, end in one of these ganglia. Those destined for the abdominal and pelvic viscera pass through

the sympathetic chain by the splanchnic nerves to termi-

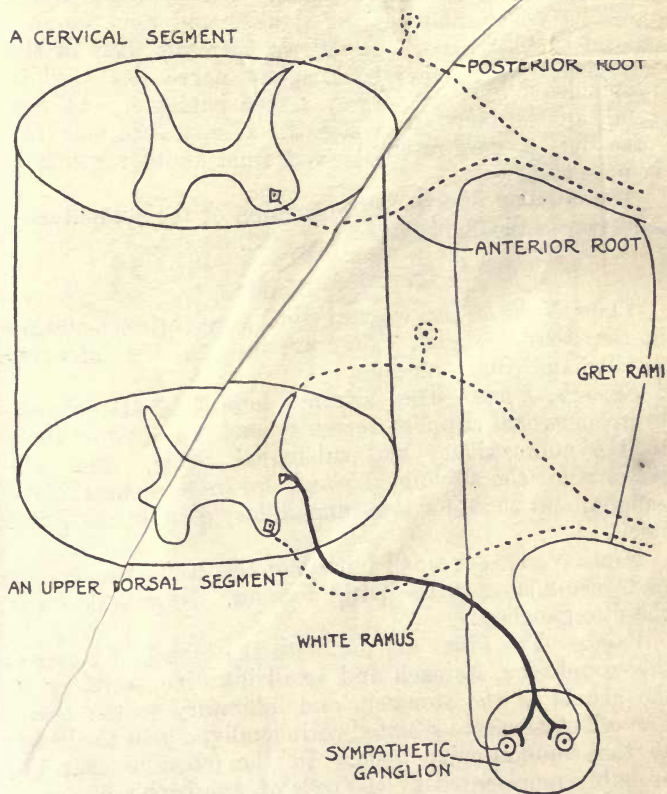


FIG. 61.—Diagram to show how a dorsal segment of the cord has both a white and a grey ramus, while a cervical segment has a grey ramus only.

nate in the collateral ganglia—the semilunar ganglion, the superior and inferior mesenteric ganglia.

All the fibres which convey impulses to the skin end in the ganglia of the lateral chain. Here post-ganglionic fibres (*grey rami communicantes*) arise and join the segmental somatic nerves. It follows, therefore, that in the thoracico-lumbar region each spinal nerve has a white ramus leaving it and a grey ramus joining it. In segments of the body from which the sympathetic does not arise only a grey ramus, derived from another segment, is present (Fig. 61).

The detailed distribution and action of the sympathetic is shown in the Table given on p. 333.

Cranial Autonomic

Third Nerve.—The visceral fibres have their cell-station in the ciliary ganglia. They are motor to the sphincter pupillæ and ciliary muscles.

Seventh Nerve.—The visceral branch is the chorda tympani which supplies secretory and vaso-dilator fibres to the submaxillary and sublingual glands. The cell-stations for the sublingual gland are in the submaxillary ganglia, and those for the submaxillary gland in the gland itself.

Ninth Nerve.—A small branch of this nerve is secretory and vaso-dilator to the parotid gland. Its cell-station is the otic ganglion.

Vagus.—The fibres are motor to the bronchial muscles, the œsophagus, stomach and small intestine, secretory to the glands of the stomach, and inhibitory to the heart. The cell-stations are situated peripherally, *e. g.* in the heart, at the sino-auricular node. In the intestine they are probably represented by the cells of Auerbach's plexus.

Sacral Autonomic

The pre-ganglionic fibres form the pelvic nerve or *nervus erigens*. The cell-stations are in the hypogastric plexus situated at the neck of the bladder. Stimulation causes vaso-dilatation of the penis (erection), contraction of the

Region.	Level of Exit from Cord.	Cell-station.	Distribution and Action.
Head and neck	Th. 1, 2, 3, 4, 5	Superior cervical ganglion	Vaso-constriction except to vessels of brain. Secretion of sweat. Erection of hairs. Dilatation of pupil and protrusion of eyeball. Secretion of saliva.
Upper limb	Th. 4-10	Stellate ganglion	Vaso-constriction. Secretion of sweat. Erection of hairs.
Thorax	Th. 1-5	Stellate ganglion	Accelerates and augments heart-beat. ? Relaxes bronchioles.
Abdomen	Th. 7-12 L. 1-4	Semilunar and superior mesenteric ganglia	Vaso-constriction of abdominal viscera. Inhibition of muscular coats of small intestine. Constricts the ileo-colic sphincter. Discharge of sugar from liver.
Pelvis	Th. 7-12 L. 1-4	Inferior mesenteric ganglia	Vaso-constriction to pelvic viscera. Inhibition of muscular coats of colon and rectum. Constriction of internal sphincter of anus. Inhibition of body of bladder. Constriction of sphincters of bladder. Stimulation and inhibition of uterus and vagina.
Lower limb	Th. 11, 12 L. 1-4	6th and 7th lumbar and 1st sacral ganglia	Vaso-constriction. Secretion of sweat. Erection of hairs.

rectum, colon and bladder, and inhibition of the neck of the bladder and internal sphincter ani.

INTEROCEPTIVE OR VISCERAL SENSATION

Compared with the exteroceptive field the interoceptive field possesses very few afferent nerves, and there are no sensory endings, free nerve-endings, or touch-spots such as are found in the skin.

Touch.—The whole of the mucous membrane of the alimentary canal, from the upper end of the œsophagus to the lower end of the rectum, is insensitive to touch.

Temperature.—The œsophagus and anal canal are sensitive to temperature, the former, like the mouth, being able to withstand a higher temperature than the skin. The stomach is usually insensitive to temperature, sensations of temperature commonly regarded as arising in the stomach being in reality felt at the lower end of the œsophagus. If two concentric tubes, one within the other, be passed into the stomach and water poured down the inner one, the subject is usually unable to tell whether the water is hot or cold. The intestine similarly is insensitive to temperature, and the colon and rectum usually so.

Chemicals.—Both the œsophagus and stomach are insensitive to dilute acids. Alcohol of 50 per cent. and glycerine cause in the stomach a burning sensation.

Pain.—The stomach and intestines, gall bladder, bile ducts and ureter are completely insensitive to pin-pricks, cuts and pinching. Sensation of pain only arises as the result of abnormal tension of the muscle-fibres. This occurs when a part of the viscus goes into spasmodic contraction, *e.g.* upon an obstruction such as a gall-stone or renal calculus, or when there is obstruction to the normal peristaltic wave of the stomach or intestine.

The sensation of fullness is caused by a mild degree of muscular tension.

Hunger.—This may be analysed into three sensations : (1) general bodily weakness ; (2) a feeling of emptiness referred to the abdomen ; and (3) hunger pains. The last come on at intervals, and are due, as Cannon has shown, to periodic contraction of the stomach wall.

From the œsophagus the afferent fibres pass up by the vagus ; from the rest of the alimentary canal, first by the sympathetic, then entering the cord by the posterior roots.

Localisation of Interoceptive Sensation. Referred Pain

Compared with sensations arising in the skin, visceral sensations are very poorly localised. Intestinal pain is felt vaguely in some region of the abdomen. But the localisation of pain is not always confined to the viscera. It is often accompanied by pain and tenderness of a certain area of skin, to which the visceral pain is said to be referred. Referred pain is felt approximately in the part of the skin which belongs to the same primitive body segment as the part of the gut from which the visceral pain arises. It is due apparently to the overflow of impulses as they enter the cord, and to the inability of the higher centres to distinguish from which part of the segment the pain arises. Pain from the stomach, for instance, is referred to the epigastrium ; pain from the ureter to the flank and groin.

CHAPTER XVI

MUSCULAR ACTIVITY AND FATIGUE

MUSCULAR ACTIVITY

WE are now in a position to piece together the changes which occur in the different organs when the body passes from a state of rest to a state of muscular activity. Upon the proper co-ordination of these changes depends the efficiency of the animal as a machine.

The repeated contraction of the muscles produces three changes in the blood flowing through them: (1) a mechanical effect, the pumping of the blood at a greater rate through the capillaries; (2) the production of metabolites, such as CO_2 and lactic acid, which have a direct vaso-dilator action upon the arterioles and capillaries; (3) a rise in the temperature of the blood.

The increase in the venous flow and the raised temperature of the blood have a direct effect upon the output of the heart, the former increasing the diastolic filling and therefore the output per beat, the latter increasing the rate of the beat. Further, the increased venous pressure causes a quickening of the beat reflexly through the vagus. The combined result is therefore a greatly increased cardiac output.

The increased hydrogen ion concentration of the arterial blood stimulates the medullary nuclei—the respiratory and vaso-motor centres. By the enhanced activity of the former the pulmonary ventilation is increased. In this way the increase in ventilation of the lungs keeps pace

with the increase in the velocity of the blood passing through the pulmonary circulation, a direct linear relationship being established between them. Incidentally the increased pulmonary movement, and especially the ascent and descent of the diaphragm, reinforce the pumping action of the muscles in driving blood to the heart.

By the stimulating action of the increased hydrogen ion concentration of the blood upon the vaso-motor centre, impulses passing along the sympathetic fibres cause vaso-constriction of the visceral organs, whereby the general blood-pressure is raised and blood is diverted in greater quantity to the organs which require it—the brain, the heart and the skeletal muscles.

These several factors combine greatly to increase the oxygen supply to the active tissues. The increased H. ion concentration of the blood facilitates the dissociation of oxyhæmoglobin, and therefore causes the blood to part the more readily with its oxygen as it passes more quickly through the capillaries.

So far we have considered the adaptation in the circulatory and respiratory mechanism only in so far as they are produced by the increased muscular activity. Were this the only causative factor, such adaptation would take some time to establish itself. Experience shows, however, that the increased blood-pressure, the deeper respiration and the quickened pulse-rate occur* within a second of the beginning of exercise. In the mental processes of concentration, therefore, impulses pass from the cerebral cortex influencing directly the medullary centres. When in an animal the lower limbs are tetanised this initial adaptation does not occur.

As the temperature of the body is raised, changes occur in the skin—dilatation of blood-vessels and secretion of sweat—which have the effect of preventing the body temperature from rising excessively.

It is well known that the maximum physical effect of which the body is capable depends upon the degree of

excitement or emotion which is the accompaniment of the exertion. Two factors seem to be responsible for this. First, the greater intensity of the mental processes means a greater outflow of impulses to the medulla—further quickening of the heart, rise of blood-pressure and depth of respiration. Secondly, it is believed that owing to sympathetic stimulation of the suprarenal glands, adrenalin is discharged into the blood. This has the effect of intensifying and prolonging the effect already produced by the sympathetic impulses to the organs themselves. By the quickened heart-beat and visceral vaso-constriction the maximum diversion of blood to the active tissues is established; by the erection of hairs and secretion of sweat there is an increase in the amount of heat lost. The metabolic needs of the active muscles are met by a discharge of glucose from the liver. It is stated, also, that adrenalin accelerates the recovery of the muscles from fatigue. In this way adrenalin completes the transformation of the resting into the fighting animal. At the end of exercise, in normal individuals the pulse and respiration rapidly subside and should reach their normal rate within five minutes.

FATIGUE

Fatigue is distinguished objectively by a diminished functional capacity, and subjectively by a general feeling of lassitude, tiredness referred to the muscles, and desire for sleep. The two problems which we have to consider are the location and the cause of the diminished capacity for work.

As to the location, this may be in any of the following structures: (1) muscles; (2) nerve endings; (3) peripheral nerve-fibres; (4) spinal nerve-cells; (5) synapses; (6) cerebral cells.

When the excised muscle is stimulated repeatedly its contraction undergoes a progressive alteration—lengthening of the latent period, slowing of the contraction, diminu-

tion in the height of contraction, and a very considerable prolongation of the period of relaxation. In fact, the muscle fails to recover its original length and undergoes gradual and permanent shortening. Eventually it fails to respond altogether: the muscle has lost its capacity for contraction.

When a muscle is made to undergo repeated *voluntary* contractions, these diminish to extinction; but when it is in this state the muscle has not lost its capacity to contract, for it responds briskly to electrical stimulation applied to the muscle itself or to its nerve. Under physiological conditions, then, loss of functional capacity is not to be entirely or even primarily located in the muscle, nor in the nerve-ending, nor, again, in the nerve-trunk. As regards the last, nerve-fibres are believed to be almost immune to fatigue.

We have seen that the reflex arc is more liable to fatigue than the nerve-fibre. This greater susceptibility of the arc must be attributable to the nerve-cell, or to the synapse, or to the receptor organ.

It is not the nerve-cell, for the *final common path* (p. 278), when stimulated to fatigue by one receptor, responds with undiminished vigour to another. Nor is there any evidence that the receptor is specially prone to fatigue. Fatigue must therefore be located in the synapses between the neurones. As to the cells of the brain, histological changes have been described in them as the result of prolonged activity. The diminished capacity to function seems, therefore, to occur in the synapses and in the higher nerve-cells.

The Cause of Fatigue.—The signs of fatigue in the nerve-muscle preparation are associated with the accumulation of lactic acid, and are, indeed, in large measure due to it, for if the muscle is perfused with a fluid not containing any food substances or oxygen, recovery ensues. If, on the other hand, fresh muscle is perfused with lactic acid, it becomes more prone to fatigue. This accumulation of

acid is, however, not the cause of fatigue, for there is a limit to which recovery can be obtained by mere removal of the acid. Under these conditions recovery can only be induced when the perfusing fluid contains food substances such as carbohydrates.

Two factors, then, are concerned in fatigue of the isolated muscle—accumulation of lactic acid and deficiency of food material. As a necessary consequence of the absence of circulating fluid, the former is the more important. To what extent is lactic acid a cause of fatigue in the muscle *in situ*?

Now lactic acid, as we have seen, is not an abnormal product of muscular metabolism but a normal intermediate product, its ultimate oxidation providing the necessary energy for subsequent activity. What is abnormal is not the formation of the acid but its accumulation due to failure of oxidation. We may therefore look to deficiency of oxygen as a cause of this accumulation. This is borne out by experimental findings in cases of muscular exercise. The appearance of lactic acid in the urine depends not upon the duration of exercise nor upon the amount of mechanical work involved, but upon the coincident respiratory distress—that is to say, owing to the call for oxygen by the tissues not being satisfied.

Provided, then, that the supply of oxygen is sufficient, there is no accumulation of lactic acid, at any rate in sufficient amount to cause overflow into the general circulation. But in the measure that oxygen fails, acid accumulates. In so far, then, as fatigue can be located in muscle, we may attribute its occurrence to accumulation of lactic acid.

As regards fatigue of the nervous system, this may be induced in the frog by depriving the spinal cord of oxygen, recovery ensuing when the cord is perfused, still in the absence of the gas. Fatigue, then, would seem to be the same process essentially, whether in the central nervous system or in the muscles.

Whether the lactic acid (or any other metabolite) affects the nerve-centres directly or whether it directly stimulates the nerve-endings is unknown.

The view is also held that fatigue is due to the mechanical stimulation of the nerve-endings consequent upon the prolonged movement.

CHAPTER XVII

REPRODUCTION

Introduction

THE capacity for reproduction is one of the principal characteristics of living matter. In the simplest forms of life it occurs in two ways. One consists merely in the division of the single-celled organism into two and the subsequent growth of these until they resemble the parent. By the repetition of this process several times a large number of individuals is formed. But sooner or later this process comes to an end, the capacity for division undergoing decay. Further propagation can only occur by a second method which consists in the fusion of two cells. By this process the reproductive function is restored, the new cell undergoing division with great vigour.

In higher animals reproduction is effected by essentially the same two processes. The repeated division which the fertilised ovum undergoes are exactly comparable with the division of protozoa, the only difference being that in the former the cells formed, instead of becoming independent, remain bound together to form the multicellular animal, the process culminating in the formation of a new individual.

The capacity for division comes to an end at different periods according to the nature of the tissue. In nerve-cells new-formation probably never occurs after birth, while in other tissues it persists throughout life. In the latter case it may be continually occurring, as in the cells

of the epidermis which are constantly being formed to make up for those shed, or it may be a function called into play only for the purpose of filling up the ranks in tissues which have been destroyed by disease. Such a process happens in the lung epithelium after pneumonia.

Death of the individual in the higher animals corresponds to the cessation of the capacity to divide in protozoa; and, as in the latter, the continuation of the race depends upon a periodic fusion of cells. But fusion as it occurs in the protozoa differs from fusion in higher forms in two important respects. First, in protozoa all the cells produced by division seem to be capable of pairing and fusing, while in the higher animals this capacity becomes the special property of a small group of cells which exist for no other purpose. As we ascend in the animal scale these cells become fewer relatively to the whole body. Secondly, while in the protozoa the two cells which fuse together appear to have identical structure, in higher forms a difference arises between them. This is associated with anatomical differences in the two individuals in which they are formed. Of these individuals one plays but a momentary part in the process of reproduction, while the other protects and nourishes the offspring until the latter is capable of an independent existence. The higher the animal the more prolonged is the period of its helplessness. The changes which take place in the reproductive process during evolution may therefore be summarised as a specialisation in certain cells of the capacity for fusion, differentiation of sex and increasing dependence of the young upon the mother.

Yet though in higher animals the sexual organs have sunk to form but a small part of the body, they exert a profound influence upon the growth and metabolism of the whole organism. We shall see how the ovary and testis pour into the blood substances the presence of which is necessary for the orderly succession of events which make up the reproductive process, beginning in the desire for

copulation and ending only when the offspring can fend for itself.

Division of Cells

Division of cells occurs by a process known as mitosis or karyokinesis. It involves the nucleus as well as the cytoplasm.

In the resting cell the nucleus is surrounded by an irregular mass of a basophile material—chromatin. In the cytoplasm is a small star-shaped body—the centrosome. Division takes place in the following stages:—

1. The chromatin is arranged in one long skein or spireme.

2. The skein divides into a number of segments which are sometimes V-shaped. These are now known as *chromosomes*. The number of chromosomes is constant for each species, the number in man being twenty-four. Meanwhile the centrosome has divided, one division migrating to the opposite side of the nucleus. The stellate appearance of the centrosomes becomes accentuated and the two become joined together by fine lines in the form of a spindle—the achromatic spindle (*Diaster stage*).

3. The chromosomes dispose themselves radially at the equator of the spindle.

4. Each chromosome divides longitudinally, the halves separating and passing to the two centrosomes. Here they join up into a skein, eventually resuming the form of the resting nucleus.

5. The spindle disappears, and at its equator the cytoplasm is modified to form a partition. In this way the division of the cells is completed.

This, the usual form, is known as **homotype mitosis**.

A modified form of mitosis, known as **heterotype**, occurs at one stage in the course of formation of the mature male and female sexual cells. The number of chromosomes into which the skein divides is only half the normal. These divide transversely, instead of longitudinally. In the male,

heterotype mitosis occurs at the formation of the spermatids, and in the female at the casting off of the second polar body. The spermatozoön and mature ovum therefore contain each of them half the amount of chromatin. At the fusion of the nuclei in fertilisation the normal amount of chromatin is restored. The reduction of chromatin is therefore a device for the prevention of the doubling of the chromosomes at each new generation.

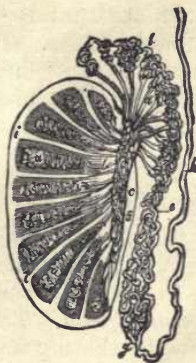


FIG. 62.—Plan of arrangement of tubules and ducts of testicle (from Schafer's *Essentials of Histology*, after Quain): *a*, seminiferous tubules; *b*, straight tubules; *c*, rete testis; *d*, vasa efferentia; *e*, *f*, *g*, epididymis; *h*, vas deferens; *i*, tunica albuginea with trabecular.

THE MALE ORGANS OF REPRODUCTION

The Testis and Vas Deferens

The testis consists of a number of seminiferous tubules grouped into lobules by strands of fibrous tissue. These strands arise from a fibrous mass called the mediastinum testis, which is situated posteriorly and is continuous with the tunica albuginea or sheath which invests the testis. In the connective-tissue between the tubules are cells of epithelioid form—the interstitial cells. The seminiferous

tubules are united posteriorly in groups to form the straight tubules which lead into the rete testis—a network of canals situated in the mediastinum. From the rete about twenty vessels known as the *vasa efferentia* lead into the canal of the epididymis. For part of their course the vasa efferentia are convoluted—the *coni vasculosi*. The **epididymis**, a tube much coiled and of great length, serves as a store for spermatozoa, and its cells contribute to the seminal fluid. It leads into the vas deferens. The vasa efferentia and epididymis are ciliated internally and their walls contain unstriated muscle fibres. The wall of the vas contains three muscular layers; its epithelium is not ciliated. The vas opens into the prostatic portion of the urethra. Shortly before its termination the *seminal vesicle* opens into it.

The Formation of Spermatozoa

Each seminiferous tubule is composed of several layers of cells enclosed in a basement-membrane. The layer next to the basement-membrane consists of cubical epithelial cells—the *spermatogonia*. These by division are continually giving rise to the next layer of much larger cells—the *spermatocytes*. Each spermatocyte divides into two daughter-cells, and each of these again into two *spermatids*. In this last division there is a reduction of the number of chromosomes (*heterotype mitosis*). The spermatids elongate, the nucleus passes to one end and a tail develops at the other. The spermatozoa as they are thus being formed lie in groups on the inner part of the tubules, their tails occupying the lumen. Accompanying each group is a cell of Sertoli, an elongated cell derived from the epithelium at the periphery of the tubule. The cells of Sertoli are believed to take part in the nutrition of the spermatozoa. The last stage is the liberation of the spermatozoa in the seminal fluid.

The various stages in the formation of the spermatozoa are represented in Fig. 64, p. 348.

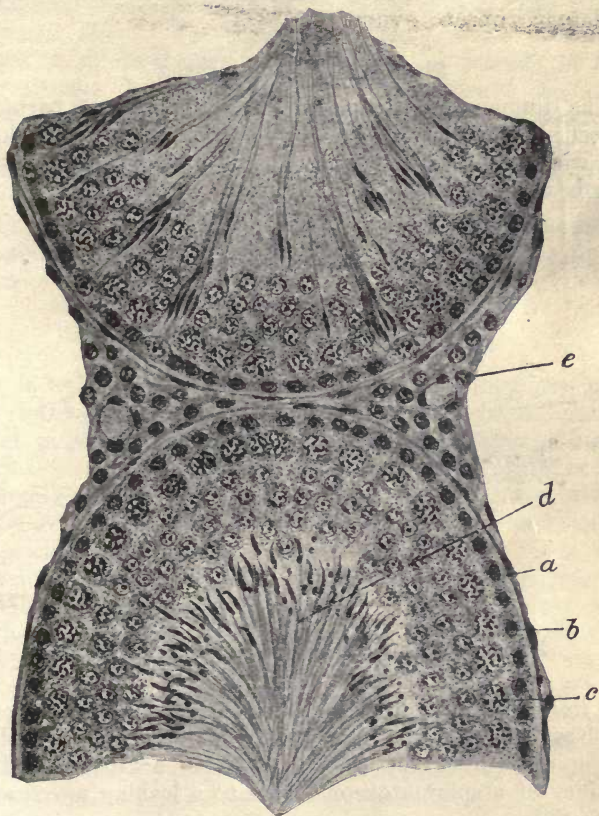


FIG. 63.—Portion of two seminiferous tubules in testis of rat: *a*, basement membrane; *b*, spermatogonium; *c*, spermatocyte; *d*, spermatozoa in cavity of tubule; *e*, interstitial tissue containing vessels (Marshall).

These changes constitute the maturation of the spermatozoa and have their counterpart in similar changes undergone by the ovum.

Structure of Spermatozoa

The human spermatozoon consists of three parts, a flattened ovoid head, a small cylindrical body, and a long tail which consists of a filament embedded in protoplasm. The head constitutes the nucleus and contains chromatin.

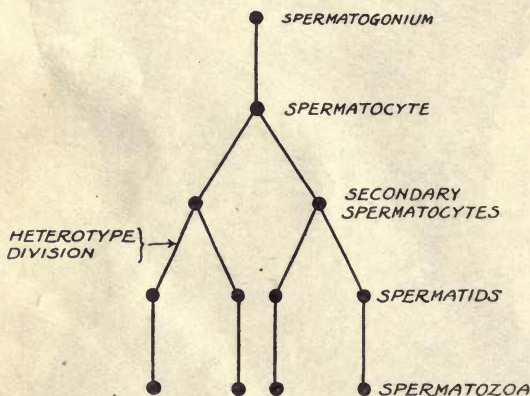


FIG. 64.—Scheme of spermatogenesis (after Boveri).

The tail runs through the middle of the body, arising from the base of the head. At the anterior part of the head is an apical projection known as the achrosome. The motility of a spermatozoon is due to a lashing movement of its tail.

Accessory Sexual Glands

The *seminal vesicles* consist of convoluted tubes opening into the termination of the vas. They secrete a fluid which nourishes and stimulates the spermatozoa.

The **prostate** consists of alveoli lined with cubical epithelium and separated by connective tissue and plain muscular fibres. The secretion of the prostate probably serves to dilute the semen, to prolong the activity of the spermatozoa by affording them nourishment and to wash out traces of urine from the urethra preparatory to ejaculation.

Concerning the function of **Cowper's glands**, which open into the urethra about two inches below the prostate, little is known. From the fact that their secretion precedes ejaculation it is suggested that they, like the prostate, serve to clean the urethra of urine.

The Internal Secretion of the Testis

It is well known that castration in the young prevents the development of the secondary sexual characteristics which normally occurs at puberty—the voice remains high-pitched; hair fails to grow on the face; there is an absence of bodily and mental vigour. The presence of the testis, therefore, exerts a profound influence upon the bodily metabolism. That this influence is brought about by chemical means is abundantly proved. The acquirement of the secondary sexual characteristics is not prevented by ligaturing the vas, nor when the testes are removed and transplanted elsewhere in the body.

Removal of the testes in the adult leads to atrophy of the seminal vesicles, prostate and Cowper's glands.

A substance having the formula $C_5H_{14}N_2$ —known as **spermine**—has been isolated and is alleged, but on unconfirmed evidence, to be the active principle.

There is some evidence that the formation of the internal secretion is the function not of the tubules but of the **interstitial cells**. After occlusion of the vas, the former atrophy, but the latter undergo no change.

The Penis

The penis consists essentially of three columns of erectile tissue—the two *corpora cavernosa* which lie side by side, and the *corpus spongiosum* which lies inferiorly and surrounds the urethra. The three corpora are surrounded by a sheath which contains white, elastic, and plain muscle fibres. Proximally, the corpora are enlarged and are surrounded by muscles, the corpora cavernosa by the ischio-cavernosus muscles or *erectores penis*, and the corpus spongiosum by the bulbo-cavernosus or *ejaculator urinæ*. At the distal end of the penis the corpus spongiosum is dilated to form the *glans penis*. The erectile tissue of the three corpora consists of a network of trabeculæ enclosing venous spaces.

Erection consists in an engorgement of the venous spaces of the corpora. It is brought about by two factors. There is an active *vaso-dilatation* of the arterioles, and a *compression of the veins* by the ischio-cavernosus and bulbo-cavernosus muscles. Erection is essentially a reflex action, for it occurs after section of the spinal cord above the lumbar region. The centre lies in the lumbo-sacral region. The afferent nerves are those arising in the glans penis. The vaso-dilator fibres (*nervi erigentes*) arise in the first and second sacral nerves. The lumbar nerves, derived from the sympathetic, which also supply the penis, are *vaso-constrictor* and therefore inhibit erection.

Erection has been produced by electrical stimulation of the crura cerebri and cord.

The **ejaculation of semen** is a reflex induced by the friction of the glans penis against the vulva. Waves of contraction pass along the epididymis and vas. At the same time there occur contractions of the seminal vesicles and prostate. The combined fluid is thus driven into the urethra. It is prevented from entering the bladder by the contraction of the sphincter. The discharge of the

semen into the vagina is due to the ischio-cavernosus and bulbo-cavernosus muscles, which undergo rhythmic contraction.

The centre controlling ejaculation lies in the lumbosacral region of the cord. The efferent fibres for the contraction of the vasa deferentia leave the cord by the second, third and fourth lumbar roots. Passing through the inferior mesenteric ganglia, they form the hypogastric nerves. The motor fibres to the ischio-cavernosus and bulbo-cavernosus muscles lie in the *nervi erigentes*.

THE FEMALE ORGANS OF REPRODUCTION

Between puberty, when the sexual organs first become active, and the menopause or climacteric (at about the forty-sixth year), when they cease to function, the ovary and uterus undergo a parallel series of cyclical changes, which are only interrupted by the more profound modifications which occur during pregnancy.

The cycle of changes, which is fundamentally the same in all mammals, is known as the **œstrous cycle**. It consists of the following phases:—

Pro-œstrum.—This is the period of uterine congestion, culminating in a discharge of blood and mucus.

Æstrus or Period of Desire.—This follows immediately upon pro-œstrum. In many mammals it is the only period during which the female evinces sexual desire and during which copulation leads to fertilisation. Æstrus corresponds in point of time to *ovulation*, to be described later.

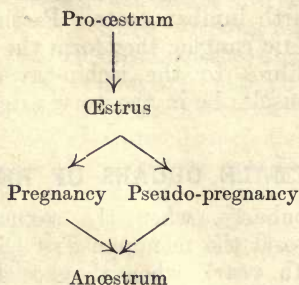
Metœstrum.—During this period the activity of the sexual organs diminishes.

Anœstrum or Period of Rest.—The sexual organs are now relatively quiescent.

Some animals—*e.g.* rabbit, bitch—may, after coitus, undergo a condition known as **pseudo-pregnancy**—the uterus, mammary gland and corpora lutea (see below)

hypertrophy until the fifteenth day and then atrophy, the animals not being pregnant.

When pregnancy or pseudo-pregnancy happen *metœstrum* does not occur. The cycle which takes place under these conditions may therefore be represented thus—



Changes in the Human Non-pregnant Uterus

The Menstrual Cycle.—The complete cycle usually occupies twenty-eight days. It is divided into four stages—

1. **Stage of Quiescence.**—This lasts about twelve days.

2. **The Constructive Stage.**—This begins with an increase in the glands and stroma of the mucous coat, accompanied by dilatation of the blood-vessels. Exudation of blood and serum occurs into the tissue-spaces. These changes are associated with a general thickening of the mucosa. The constructive stage lasts about five days.

3. **The Destructive Stage—Menstruation.**—This begins with free extravasation of blood into the stroma, due partly to diapedesis, partly to rupture of the capillaries. The blood accumulating under the epithelium breaks through into the lumen, blood and epithelial cells being discharged from the vagina mixed with mucus from the enlarged glands. The average duration of the menstrual flow is four days. This period is accompanied by a general bodily disturbance—lassitude and pains in the back.

4. **Stage of Repair.**—Lasting about seven days, this stage consists in a regeneration of the mucosa, contraction of blood-vessels and reabsorption of blood which has not been discharged.

It is clear from what has been said above that the menstrual cycle is but a form of the œstrous cycle. We may thus synchronise the process as it occurs in women with the general type appertaining to all mammals.

<i>Stage of Quiescence</i>	}	Anœstrum.
<i>Constructive Stage</i>		Pro-œstrum
<i>Destructive Stage (Menstruation)</i>		
<i>Stage of Repair</i>	{	œstrus
		Metœstrum

In civilised mankind œstrus has practically disappeared, but it still persists in primitive races.

The significance of menstruation and its correlation with the changes which occur in the ovary will be discussed later.

The Ovary

The ovary consists of a stroma of fibrous tissue with unstriped muscle-fibres and blood-vessels. It is covered by a single layer of epithelial cells—the **germinal epithelium**. Lying in the stroma are a large number of vesicles of varying size—these are the **Graafian follicles** in different stages of development. Each follicle contains an ovum. There occur also the corpora lutea, or discharged follicles.

Ovulation and Maturation

During sexual life the ovary undergoes a cycle of changes concurrent with those occurring in the uterus. These consist in the hypertrophy of one or more follicles. At an early stage the follicle consists of the ovum surrounded by a single layer of epithelial cells. Immediately around it the stroma is condensed to form a sheath. The growth

of the follicle is due to the proliferation of the epithelial cells. These eventually form two layers—the *membrana granulosa* lining the cavity and the *discus proligerus* covering the ovum. These two layers become partly separated by the gradual accumulation of fluid—*liquor folliculi*. Hypertrophic changes simultaneously occur in the fibrous sheath, in which two layers become recognisable—*theca externa* and *theca interna*.

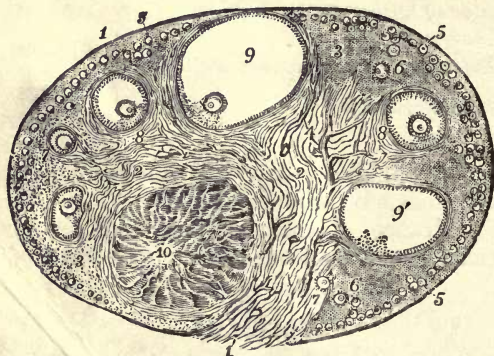


FIG. 65.—Section of cat's ovary (Schron), from Schafer's *Essentials of Histology*, after Quain: 1, germinal epithelium; 5, Graafian follicles in their earliest stages; 6, 7, 8, more advanced follicles; 9, almost mature follicle; 10, corpus luteum.

The ripe follicle has a diameter of 15 mm. and protrudes from the surface of the ovary.

The ovum consists of a single cell containing nucleus and nucleolus. It is surrounded by a thin membrane—the *vitelline membrane*, around which is the *zona radiata*, a radially striated structure which is supposed to contain fine canals through which the ovum is nourished.

The growth of the follicle culminates in its rupture, the ovum, surrounded by the *discus proligerus*, being discharged into the peritoneal cavity. This process, which is known as ovulation, occurs regularly at oestrus in most

mammals, but in some—*e. g.* the rabbit, cat—only as the result of copulation. Failing copulation in these animals the follicle undergoes atrophic changes. Upon the discharge of the ovum, the fimbriæ of the Fallopian tube are erected around the ovary, and by their muscular and ciliary action sweep the ovum into the tube.

While these changes are taking place the ovum undergoes the process of **maturation**. The ovum divides by karyokinesis, the cleavage being very unequal. The smaller product is extruded upon the surface of the ovum and is known as the *first polar body*. This may later divide into two. The ovum then forms a *second polar body*, but in this division the number of chromosomes is reduced by a half. The nucleus of the matured ovum is known as the *female pronucleus*.

The process of maturation may be thus represented:—

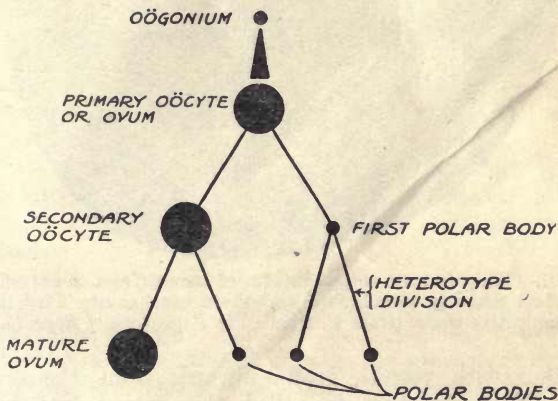


FIG. 66.—Maturation. Compare with Fig. 64, p. 348.

In the male all four products of division become functional reproductive cells; in the female this happens only to one, the others playing a subsidiary rôle.

The Corpus Luteum

When the ovum has been discharged the epithelial cells which remain in the Graafian follicle hypertrophy and form a solid mass of large cells containing a yellow pigment—**lutein**—and separated by connective tissue which,

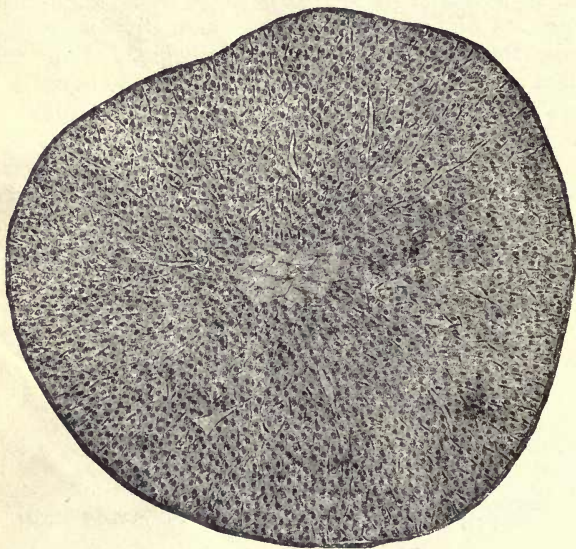


FIG. 67.—Fully formed corpus luteum of mouse (from Sobotta). The luteal tissue is vascularised and the central cavity filled in with connective-tissue (from Marshall, *The Physiology of Reproduction*).

together with vessels, grows inwards from the outside wall. This structure is called the **corpus luteum**. In the centre there may be a clot of blood caused by the rupture of the blood-vessels during ovulation. If pregnancy does not occur the corpus luteum in some animals grows only for a short period, then atrophies. But if conception takes place its growth continues until the middle

of pregnancy, when it attains a diameter of about half an inch. This size is maintained—at any rate in the rabbit—until a late period of gestation or even into lactation. It then undergoes degeneration and becomes transformed into interstitial tissue. *The persistence of the corpus luteum is dependent upon the presence of the fœtus in the uterus* in all those animals such as Man which do not experience pseudo-pregnancy.

In animals which do experience pseudo-pregnancy (p. 351) the corpus luteum persists for a period as long, or almost as long, as in true pregnancy.

Internal Secretion of the Ovary

When both ovaries are excised in early life the changes characteristic of puberty do not occur. There are no œstrous cycles, the uterus remaining in an infantile condition. Secondary sexual characteristics fail to appear, there being in some animals an approach to the male physical form.

On removal of the ovaries after puberty, menstruation ceases, while the uterus, and sometimes the breast, undergo atrophic changes.

In some animals the ovaries have been removed and other ovaries grafted. Under these conditions follicle-formation occurs in the graft and the œstrous cycle is resumed.

Any reflex connection between the ovarian and uterine changes is out of the question. This is proved not only by the transplantation experiments mentioned above, but also by the fact that the changes in the uterus occur when all nervous connection with the ovary is destroyed by removal of the lumbo-sacral part of the cord.

The ovary therefore produces a *hormone* which is necessary for the nutrition of the uterus. As the ovary undergoes its cycle of changes it is probable that the secretion varies in amount, and that this variation determines the parallel cycle of changes in the uterus.

The hormone responsible seems to be produced either in the epithelial or in the interstitial cells. There is some positive evidence that it is independent of the corpus luteum.

Function of the Corpus Luteum

The corpus luteum is believed to furnish a hormone which is responsible for the changes in the uterine wall which occur during the early stages of pregnancy and which are necessary for the proper nutrition and fixation of the embryo. When the ovaries are removed early in pregnancy abortion occurs, but when the operation is performed at a later period there is no interruption of the normal course of events.

In pseudo-pregnancy the uterus undergoes very pronounced hypertrophy, congestion and great glandular development under the influence of the corpus luteum in just the same way as happens during true pregnancy. Moreover, after a mechanical stimulus (introduction of a foreign body or incision of the wall), decidua cells are formed, but only if corpora lutea are present in the ovary.

The corpus luteum is also considered responsible for a hormone which initiates the hypertrophy of the mammary gland. This is discussed more fully later.

Correlation of the Ovarian and Uterine Cycles

There is no certain clinical evidence to show whether in women the process of ovulation precedes, succeeds or is coincident with menstruation. But the identification of menstruation with the period of pro-œstrum, and the known synchronisation of the subsequent period of œstrus in lower animals with the ripening of the follicle, are strong arguments in favour of menstruation preceding ovulation. On this view the purpose of menstruation is a kind of freshening up of the uterine mucosa preparatory to the reception of the fertilised ovum. In some animals rupture of the ripened follicle occurs only as a reflex effect of

copulation. It is probable that in women the period immediately following menstruation, corresponding to œstrus in lower animals, is the only period during which fertilisation can occur. The descent of the ovum down the Fallopian tube coincides with the ascent of the spermatozoa.

Fertilisation

During coitus the spermatozoa deposited in the vagina are sucked into the uterus by peristaltic contraction of this organ initiated reflexly by contact with the male, the efferent path being the sympathetic. They travel up into the Fallopian tubes, overcoming by the propulsive action of their tails the downward current produced by the cilia of the female passages. In the tube they meet the matured ovum on its way down from the ovary.

Of the many million spermatozoa which enter the female organs only one enters the ovum.

After impregnation, the tail is absorbed and the head, now known as the *male pro-nucleus*, fuses with the female pro-nucleus. In this process the number of chromosomes, which in each element has been reduced by a half during maturation, is restored to the number characteristic of the species. The nucleus thus formed is called the *segmentation-nucleus*. From the fertilised cell or oöperm arises the new generation.

CHANGES IN THE PREGNANT UTERUS

As the fertilised ovum passes down the Fallopian tubes changes occur in the mucous membrane of the uterus, preparatory to the embedding of the ovum within it. The stroma becomes transformed into a mass of **decidual cells**—large cells with small nuclei. The glands enlarge, the epithelium proliferates, and the blood-vessels are dilated. In this way the inucous membrane becomes greatly thickened.

By the time it reaches the uterus the ovum has develop-

as far as the **blastocyst** stage (see Fig. 68). It is a mass of cells containing a vesicle. In this form the ovum *buries itself in the decidua*. As the embryo increases in size it projects into the cavity of the uterus. In the decidua three parts are now distinguished: (1) the *decidua*

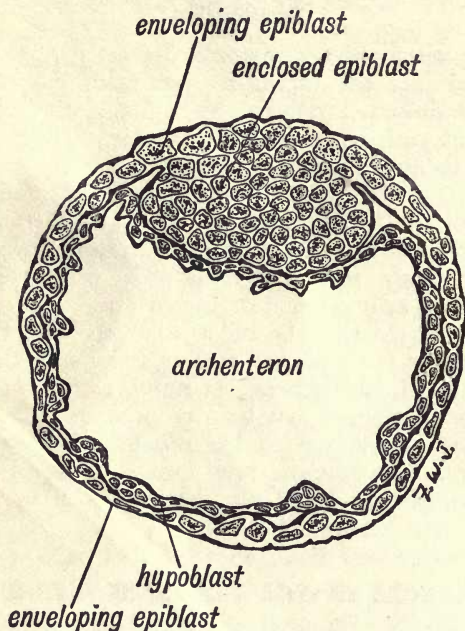


FIG. 68.—Bilaminar blastocyst (Keith, after Van Beneden).

serotina or *basalis*, where the embryo is attached to the uterus; (2) the *decidua reflexa*, which covers the embryo; and (3) the *decidua vera*, which lines the remainder of the uterine cavity. With further growth the decidua reflexa and the decidua vera come into direct contact (Fig. 69).

At an early stage the nutrition of the embryo is prob-

ably derived directly from the decidual cells and uterine glands.

Soon, however, the outermost layer of the embryo becomes specialised for the provision of nutrition—for this reason it is called the **trophoblast**. The trophoblast,

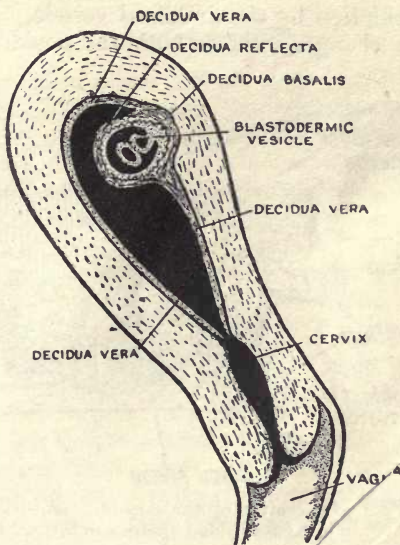


FIG. 69.—Diagrammatic section of the pregnant uterus to show the three parts of the decidua (Keith).

and a layer of mesoblast which surrounds the embryo together form the **chorion**. This becomes divided into two layers: (a) the *Basal* or *Langhan's layer* on the inner side, and (b) the *Syncytium*, a mass of protoplasm containing nuclei but no proper cell divisions. The syncytium is powerfully phagocytic. It invades the decidua, eroding not only the decidual cells but also the walls of the capillaries. The maternal blood oozes into the

eroded spaces, where it comes to lie in contact with the syncytium.

Internal to the basal layer is a layer of mesoblast. These two layers send out processes which ramify in the syncytium to form the **chorionic villi**. In the mesoblast are laid down blood-vessels which become connected with the foetal circulation by the umbilical vessels.

The above changes involve both the decidua serotina

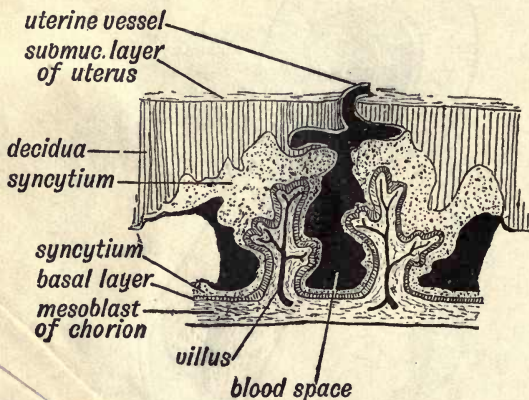


FIG. 70.—Diagrammatic section of the decidua serotina and chorion to show how the placental blood spaces are formed (Keith).

and the decidua reflexa. In the third month the hypertrophy of the chorionic villi in the former and their atrophy in the latter lead to the formation of the **placenta**.

In the fifth month the growth of the villi ceases and in place of the basal layer and syncytium there appears a single layer of flattened cells. On one side of this membrane is the foetal blood circulating in the chorionic villi, on the other side is the maternal blood circulating in the lacunæ eroded out of the decidua by the syncytium. Across the membrane the food material and oxygen are transferred from

the mother to the offspring, and the waste products from the offspring to the mother. It is important to realise that there is no mixing of the maternal and foetal blood.

The growth in size of the uterus as pregnancy proceeds is due largely to the elongation and thickening of the muscle fibres.

PARTURITION

Pregnancy lasts about 280 days and is terminated by the expulsion of the foetus. Throughout pregnancy the uterus undergoes slight contractions which are not felt by the mother. As the uterus reaches its maximum growth these contractions become gradually stronger and more frequent. At the onset of labour they increase further in intensity and frequency, and are accompanied by pain which eventually becomes extreme. Labour is technically divided into three stages. The first is the dilatation of the os uteri, due to contraction of the longitudinal uterine muscles. The second is the expulsion of the foetus. The third is the detachment of the placenta from the uterine wall and its expulsion. The second and third stages are brought about by the combined contraction of the longitudinal and circular muscles of the uterus and of the muscles of the abdominal wall. As the contents of the uterus become smaller the uterine muscles after each contraction remain at their shortened length.

Parturition can occur in animals after section of the thoracic region of the cord, and in women suffering from complete paralysis of the lower limbs. For its proper performance the integrity of the lumbar part of the cord appears to be essential, but in some animals it occurs, though often imperfectly, after complete destruction of the lower part of the cord. Under these circumstances parturition occurs through the uterine contractions only, the abdominal muscles play no part. Normal parturition is therefore due partly to the inherent rhythmicity of the uterus and partly to reflex contraction. The function of the spinal

centre is to co-ordinate the contractions of the abdominal muscles with those of the uterus.

THE FŒTAL CIRCULATION

The oxygenated blood from the placenta travels by the umbilical veins and reaches the inferior vena cava either through the liver or directly through the ductus venosus. In the inferior vena cava it becomes mixed with the venous blood returning from the lower limbs. Entering the right auricle, it is directed across that chamber through the *foramen ovale* into the left auricle—from there into the left ventricle and aorta. This blood supplies chiefly the head, neck, and upper limbs. The venous blood from these parts is collected in the superior vena cava. It passes through the right auricle into the right ventricle. From this chamber it passes by the pulmonary artery and ductus arteriosus into the descending aorta, by which it reaches the abdomen, lower limbs and placenta (by the umbilical arteries). The special features to note are :— (1) Very little blood traverses the lungs. (2) In the right auricle there are two independent currents of blood, one from the inferior vena cava to the left auricle, the other from the superior vena cava to the right ventricle. The two streams are kept apart by the Eustachian valve. (3) Blood leaves the heart in two degrees of purity—the more oxygenated blood from the left ventricle which supplies the upper part of the body, and the venous blood from the right ventricle which supplies the abdomen and lower limbs. (4) No part of the fœtus receives fully-oxygenated blood, since the blood which leaves the placenta is mixed with that which is returning from the lower part of the body of the fœtus.

The expansion of the lungs which occurs at the first inspiration determines a flow of blood from the right ventricle into the lungs and from the lungs into the left auricle. The *foramen ovale* between the auricles is a valvular arrange-

ment which permits the flow of blood only from right to left. The increased pressure in the left auricle closes the valve, which is soon sealed. The placental circulation ceases owing to the ligature of the umbilicus. Finally, the lumina of the ductus arteriosus and ductus venosus become obliterated.

LACTATION

The Mammary Glands

These consist of a number of lobes subdivided into lobules. The lobules are composed of alveoli, separated by connective tissue. From the alveoli run ducts which join together to form the *lactiferous ducts*, of which about fifteen or twenty open on the nipple. At their proximal ends the lactiferous ducts are dilated so as to allow of the accumulation of milk in the intervals between suckling. Some unstriped muscle fibres are found in the walls of the ducts. The gland owes its rounded appearance to a layer of fat which lies between it and the skin. It is plentifully supplied with blood-vessels and nerves.

The nipple is an erectile organ containing unstriated muscle fibres. On its surface are papillæ connected with sensory nerves.

The secretory cells lining the alveoli form a single layer. Their appearance varies according to the physiological condition of the gland. When the gland is at rest they are flattened, when it is active they are columnar. They contain protein granules and fatty globules. The latter are found also in the lumen of the alveoli, together with free granular cells.

The act of secretion is provoked directly by the negative pressure produced in suckling, aided probably by reflex contraction of the unstriped muscle. The lactiferous ducts are kept patent in face of the pressure of the suckling's lips owing to the nipple becoming erectile. During suckling the vessels of the gland are reflexly dilated.

Growth of the Mammary Glands

The glands undergo a slight increase in size at puberty, and a further temporary increase coincides with the menstrual periods.

The enlargement at pregnancy begins (in multiparæ, or those who have been previously pregnant) soon after the second month, in virgins immediately after conception; the nipples at the same time become pigmented. During the latter stages of pregnancy a clear fluid known as *colostrum* can be squeezed out.

The growth of the gland at puberty is due to an internal secretion elaborated by the ovary, for it does not occur when the ovaries are removed. The congestion which occurs with menstruation also appears to be of ovarian origin.

The hypertrophy of pregnancy, similarly, is not due to a nervous influence, for it occurs when all nervous connection between the pelvic organs and breasts have been severed by transection of the spinal cord.

In the first half of pregnancy mammary growth is due to a hormone poured into the blood by the corpus luteum. The continued development of the glands in the second half of pregnancy is also due to the corpus luteum, the *persistence* of which probably depends upon the presence of the foetus.

Since no secretion occurs until after parturition, it is held that the responsible hormone, at the same time as it stimulates the growth of the gland, inhibits its activity. On the removal of this inhibiting agent secretion occurs. However that may be, the secretion, when once started, depends for its continuance upon the act of suckling. It is also readily influenced by nervous agencies. The flow of milk ceases at the onset of a new pregnancy.

Composition of Milk

Milk is amphoteric in reaction and has a specific gravity lying between 1.028 and 1.034. From the following Table

it will be seen that human milk contains less protein but more lactose than cow's milk.

	Cow's.	Human.
Water	88.3	88.8
Proteins	3.0	1.0
Fats	3.5	3.5
Lactose	4.5	6.5
Salts	0.7	0.2
	<hr/> 100.0 <hr/>	<hr/> 100.0 <hr/>

The proteins are three in number—*caseinogen*, *lactalbumin* and *lactoglobulin*. It is the first which is precipitated by rennet-ferment, being converted into casein and leaving whey.

Of inorganic salts, milk is rich in calcium and phosphorus but is almost completely deficient in iron, the infant apparently relying during suckling upon the iron which is present in high percentage in the liver.

Immediately after parturition the gland secretes colostrum. This differs from milk in being a clear fluid containing very little caseinogen. It coagulates on boiling, and contains characteristic granular corpuscles which stain with osmic acid. These are probably leucocytes.

Interaction of the Female Sexual Organs

The interaction between the uterus, ovary and mammary gland may be thus summarised:—

In the first half of pregnancy the presence of the corpus luteum determines, on the one hand, the hypertrophy of the mammary gland, and on the other, the fixation and early nutrition of the foetus through the formation of the decidual cells.

In the second half of pregnancy the foetus influences the corpus luteum, and this in turn causes the further development of the mammary gland.

CHAPTER XVIII

DEFENCE

MOST of the diseases to which animals are liable are due to the invasion of the body by micro-organisms. It is familiar to every one that when an epidemic occurs, of the many who are exposed to the infection, not all take the disease; some are naturally or innately immune. Of those who take the disease a number, in most cases the greater number, recover; those who recover are for a certain period or for ever insusceptible to the disease. They have acquired immunity.

The micro-organisms owe their effects to the toxins or poisons which they produce. Immunity, whether natural or acquired, consists in the prevention of the propagation of the organisms, the neutralisation and excretion of their toxins, and the repair of damaged tissue.

The methods by which the animal overcomes the action of bacteria are seen at their simplest in lower forms of life. Unicellular organisms, such as *Amoeba* and *Paramoecium*, live upon bacteria. They ingest them and subject them to the hydrolysing action of their proteolytic enzymes. On this account *Amoeba* and *Paramoecium* are practically immune to bacteria.

If we now pass to the simpler multicellular animals we find a reaction of a slightly more complicated kind. Let us take the developing starfish in the *Gastrula* stage. The body consists of an invaginated cup, the outer layer being the ectoderm, the inner the endoderm. Between them is the body-cavity in which float free mesoblastic

cells. When a foreign body is introduced into this cavity there is a new formation of mesoblastic cells. These cells are attracted to the foreign body; they surround it, and if it is of protein nature they digest it. The attraction of the cells towards the foreign body is known as **Chemiotaxis**. It corresponds to the movement of amoeba towards its food. It will be seen that the gastrula has in this respect advanced beyond amoeba in two ways, in the specialisation of certain cells for the purpose of defence, and in the reproduction (proliferation) of the cellular defending agents.

The response to invasion is essentially the same in higher animals. Certain cells, the phagocytes, are the defending agents, and they destroy the bacteria by intracellular digestion. The greater complexity of the process in the higher animals is due to the more complicated manner in which the phagocytes are mobilised in large numbers to the site of infection. There is also a further difference. In the course of evolution host and parasite have, as it were, developed together. Each has become in some degree immune to the other. In some cases they may live in **symbiosis**, each deriving some benefit from the other. The bacilli which inhabit the large intestine of the horse live upon the cellulose which the horse eats. Owing to the bacterial liquefaction of the cellulose the horse is enabled to absorb nutriment from the grasses. But there is not always this mutual advantage. The host may tolerate the presence within it of certain bacteria. Yet under certain conditions these same bacteria may cause fatal illness. The respiratory passages of human beings are the normal habitat of the pneumococcus. It is only when the natural resistance to this organism is lowered, as by exposure to cold, that the pneumococcus produces an acute inflammation of the lungs.

When pathogenic organisms are introduced into the body the phagocytes acquire an **adaptation** to them. At first the cells are repelled (**Negative Chemiotaxis**); then

they are attracted towards the bacteria (**Positive Chemiotaxis**). They attempt to ingest them, but the reproductive and toxic powers of the latter prove too strong for them and they succumb. Phagocytes arriving later upon the scene of action are endowed with stronger properties and succeed in destroying the bacteria. While the capacity for defence is thus being gradually acquired, the infected individual runs through the course of the disease, and it is owing to the development of the mechanism of defence that he recovers.

The changes which result from infection may be readily followed in a thin vascular tissue. The first change is a dilatation of capillaries, accompanied, however, by retardation of the blood-stream. Leucocytes pass by diapedesis through the capillary walls, accompanied by an excessive flow of lymph which distends the intercellular spaces. This reaction is known as **inflammation**. It was recognised by the ancients by its four signs—**rubor, tumor, dolor** and **calor**; rubor, the redness due to the capillary dilatation; tumor, the distension and puffiness of the tissue due to the exudation; dolor, the pain produced by irritation of the nerve-endings; calor, the increased warmth of the part due to the dilatation of the vessels.

The essential features of the inflammatory process are the effusion of lymph whereby the toxins are diluted, and the mobilisation of leucocytes whereby the bacteria are ingested. The infected region becomes a mass of bacteria and cells floating in lymph. Of the cells, some are the proper cells of the part in different stages of degeneration. Some are the leucocytes, those in the centre of the mass being dead, while those situated peripherally are ingesting the bacteria. If the diseased area is small in extent all the dead cells and bacteria will be absorbed by leucocytes. If it is large, absorption will take place only to a limited degree, there remaining a central dead mass cut off from the supply of blood and surrounded by a capsule of newly formed fibrous tissue laid down by cells known as fibro-

blasts. This is an **abscess**, and the dead material which it contains is known as pus. An abscess usually ruptures on the surface of the body and its contents thus discharged. Its walls collapse, further development of fibrous tissue leading to the formation of a scar. Finally, the rent in the skin heals by new growth of epithelium.

The cells which are actively engaged in the inflammatory process may be divided into two groups: (1) those normally present in the blood in considerable number; (2) those formed from connective-tissue in general and relatively scanty in the blood. Of the first group the most important are the **polymorphonuclear leucocytes**. These are the *Microphages* of Metchnikoff. They are present in great numbers in all acute infections, and are at the same time greatly increased in number in the blood. They are actively amoeboid and digest the bacteria. In certain infections the coarsely granular eosinophiles are increased, but the function of this type of leucocyte is not properly understood. The *lymphocytes* appear to play no part in acute infections, but they are increased in chronic conditions such as tuberculosis. What part they play is not known; their phagocytic powers are very feeble.

The cells of the second group are of three kinds:—

(a) **Endothelial** (hyaline, mononuclear) cells present in very small numbers in the blood. They arise from the endothelium of serous cavities and of blood-vessels when these are infected. Metchnikoff called them *Macrophages*, and believed that they devour especially the microphages which have succumbed to the bacteria.

(b) **Fibroblasts**.—These are spindle-shaped cells arising in and forming fibrous tissue.

(c) **Plasma cells**.—These are small cells resembling and probably identical with lymphocytes.

We have said that bacteria owe their deleterious effects to the chemical action of the toxins which they form. Bacteria may be divided into two classes. In the first class

are those which remain localised in one part of the body and secrete a great quantity of powerful toxin which circulates in the blood. It is through the generalised effect of their toxins that they kill. Such are the bacilli of diphtheria and tetanus. In the other class are those which have a greater capacity for reproduction and become disseminated through the body. Their capacity to form diffusible toxin is much smaller than in members of the first class. The toxins are therefore not found in any quantity away from the bacteria themselves. The greater number of bacteria belong to this class: *Bacillus Typhosus*, *Bacillus Coli*, *Pneumococcus* and many others. It is sometimes stated that the first class form ectotoxins, the second endotoxins. Probably both classes produce ectotoxins, the difference being one of degree of diffusion of the toxin.

In order that we may understand how the body protects itself against the harmful effects of toxins, let us first consider how it behaves towards poisonous substances of simple and known constitution. In the chapters on Metabolism we have come across several instances where the absorption or injection of a substance leads to the excretion of that substance by the kidney in a combined form which is not toxic. When phenol, scatol or indol enter the blood-stream they are excreted as the non-toxic sulphates. Organic acids, such as aceto-acetic acid are excreted as the ammonium salt. Such a mechanism is known as **Protective Synthesis**. The most instructive example for our present purpose is the excretion of benzoic acid combined with glycine to form hippuric acid. Benzoic acid is toxic because it has an affinity for some essential chemical grouping of the living cell. By combination with glycine this affinity can be satisfied. Now when a certain dose of benzoic acid is administered, glycine is produced far in excess of the amount required to combine with the benzoic acid. Here, then, the body produces a protective substance and produces this substance in excess. Let us now compare with this simple instance the behaviour of

the body towards a toxin of complex and unknown structure. When an animal is repeatedly injected with a non-lethal dose of diphtheria toxin it becomes immune to a dose of the toxin many hundred times the strength of what would have been originally a fatal dose. Further, the serum of the animal thus artificially immunised, when injected into a normal animal, confers upon the latter an immunity. This is the basis of the modern treatment of diphtheria and of tetanus. As when hippuric acid is administered, the body has produced a protective substance—**an antitoxin**—and has produced this antitoxin in excess. The difference between the two cases is that no toxin or combination of toxin with antitoxin can be detected in the urine. It therefore appears that in the two cases the mechanism of defence is essentially the same, the apparent difference between them being explained by the fact that in one case the molecules concerned, being small, diffuse through the kidney, while in the other case the molecules, being large, remain in the blood and accumulate there.

Ehrlich has given a graphic representation of the formation of antitoxin. He conceives the cell protoplasm as having a number of different unsatisfied affinities which he calls **receptors**. To one of these receptors a particular toxin fits as a lock fits a key, and when it is thus fixed it kills the cell. It is quite clear that a toxin can only kill a tissue by entering into chemical combination with some component of its structure. Tetanus toxin attacks the nervous system. When an animal has died of tetanus the toxin can be recovered from every tissue except nervous tissue. It has combined with the nervous tissue to form a permanent compound. According to Ehrlich, when a non-lethal dose of toxin is administered, the tissue which is susceptible to that toxin is stimulated to produce the corresponding receptor in great numbers and to cast them off into the body-fluids. The result is that when a second dose of toxin is given, the molecules combine with the free receptors and the cell protoplasm is unaffected (Fig. 71).

When a toxin is heated to 60° it loses its toxic power but still retains the capacity to form an antitoxin when injected. Thus modified it is known as a **toxoid**. It is therefore believed that a toxin contains two molecular groups, one the **haptophore** which unites with the receptor of the protoplasm, the other the **toxophore** group which can only exert its action when the haptophore group is linked to the cell. In the toxoid the toxophore group only

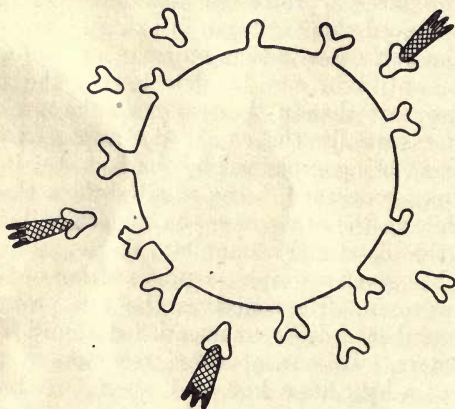


FIG. 71.

is destroyed, the haptophore group being still capable of stimulating the production and liberation of receptors (Fig. 72).

From the fact that the capacity to induce the formation of neutralising substances is found in such widely differing substances as benzoic acid and bacterial toxins, it is not surprising to find this property widely possessed by many other classes of substances. Any substance which has this property is called an **antigen**, and the substance produced in the body, an **antibody**. Any foreign protein, for instance,

when injected into the blood causes the appearance in the blood of a substance known as a **precipitin**, which precipitates that protein. This reaction is highly specific. When the serum of an animal of species A is injected into an animal of species B, the latter develops a precipitin for the serum of species A only. Upon this fact is based an important medico-legal test for human blood. There are also **agglutinins** which cause a clumping together of bacteria. Further, when foreign cells are introduced there are developed anti-

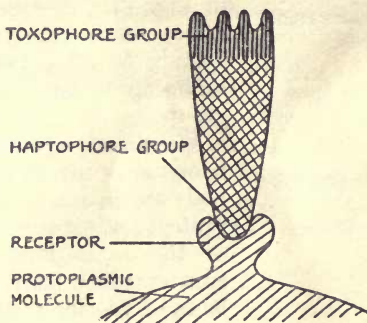


FIG. 72.

bodies—**cytolysins**—which destroy those cells. The most important of these are the **hæmolysins** which are produced on the injection of foreign red blood corpuscles. The mechanism in this case is rather complicated. Let us take a specific example.

The red blood corpuscles of the rabbit added to the normal serum of the goat are hæmolysed, but if the serum has been previously heated to 60° hæmolysis does not occur. If, however, the red blood corpuscles of the rabbit be added to the heated serum of the goat together with normal (unheated) rabbit's serum, hæmolysis results. Ehrlich believes, therefore, that there are two substances responsible,

to which he has given the names **amboceptor** and **complement**. The amboceptor (immune or intermediate body) is a specific substance not destroyed by heat. The complement (or alexin) is a specific substance destroyed by heat. It is present in nearly all sera. It is the complement which has the hæmolytic action. The amboceptor has two affinities, one for the red blood corpuscle, the other for the complement. The complement combines with the proto-

plasm only through the amboceptor. This is shown graphically in Fig. 73. It will be seen that in a sense complement corresponds to the toxophore and amboceptor to the haptophore group.

When an emulsion of dead bacteria is introduced into the body antibodies are formed which protect against any living bacteria of the same kind which may gain entrance later. This is the basis of vaccine treatment. But the immunity thus conferred is not always entirely due to the formation of antibodies. Another class of substances is developed.

These are the *Opsonins*, the

action of which is to stimulate the leucocytes to devour the bacteria.

To conclude this brief account of the reaction of the body to the invasion by foreign substances, we may mention a reaction of a different kind—**Anaphylaxis**. If 5 c.c. of egg-albumen be injected into a guinea pig, no ill effects follow, but on giving a second dose the animal becomes violently ill and usually dies within a minute or two. This curious reaction has the following characteristics: (1) The first dose may be very minute, as little

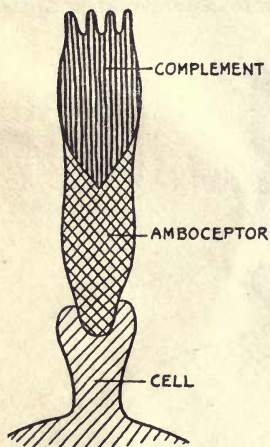
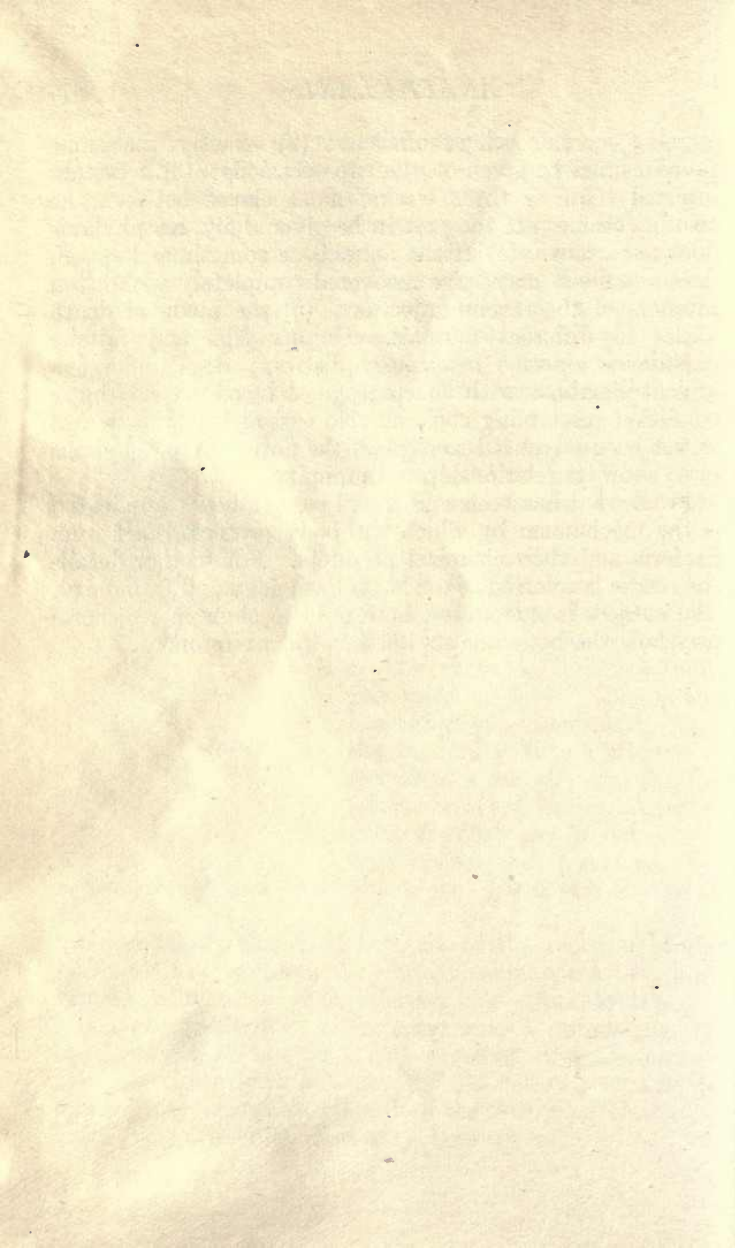


FIG. 73.

as $\frac{1}{1000000}$ c.c. being sufficient; (2) exactly the same protein must be given on the two occasions; (3) a certain interval (two or three weeks) must elapse between the two injections. If the protein be given daily, anaphylaxis does not occur. (4) If the animal, as sometimes happen, does not die it may have recovered completely within ten minutes of the second injection; (5) the mode of death varies in different animals. Guinea pigs and rabbits experience extreme respiratory distress; dogs undergo a violent diarrhœa, with the passage of blood per rectum, a condition resembling cholera. No satisfactory theory has as yet been advanced to explain the nature of anaphylaxis or to show its relationship to immunity.

From what has been said it will be seen how complicated is the mechanism by which the body protects itself from bacteria and their chemical products. For further details the reader is referred to works on Pathology and Immunity. The subject is introduced here only to show in a general way how the body adapts itself to its environment.



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